Health Policy Advisory Committee on Technology

Technology Brief Update

Microbial sealant to reduce surgical site infections following cardiac surgery

November 2014
Microbial sealant to reduce surgical site infections following cardiac surgery update: November 2014

TECHNOLOGY BRIEF UPDATE 2014

Technology, Company and Licensing

Register ID WP102
Technology name InteguSeal® microbial sealant
Patient indication Patients undergoing cardiac surgery

Reason for assessment

In 2012, a Technology Brief was completed to investigate the use of InteguSeal® microbial sealant during cardiac surgical procedures. In light of developing evidence on the subject, the Brief recommended that this technology be monitored for 24 months. In line with this recommendation, the purpose of the current Update is to consider the evidence that has emerged since 2012, and determine whether this new evidence may provide additional information to inform policy decisions.

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.1,2 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.3

SSIs are the third most frequently reported hospital acquired infection (HAI), and are the most commonly acquired in surgical patients.2,4 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. Patient specific risk factors for SSI include obesity, smoking and alcohol consumption.2

A strategy to reduce the incidence of SSIs is the minimisation of bacterial contamination at the surgical site. Standard practice involves patient skin preparation with an appropriate antiseptic agent. While effective preparation can reduce skin bacterial counts by 80 per cent, some organisms persist.4 Administration of prophylactic antibiotics has additionally reduced postoperative infection rates; however, increased use of antibiotics can result in the emergence of antibiotic-resistant pathogens.2

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.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.\textsuperscript{3,9,10} In its polymerised form, InteguSeal® is able to seal micro-abrasions on the skin and can prevent potential pathogen recolonisation.

**Stage of development in Australia**

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

**Australian Therapeutic Goods Administration approval**

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

**ARTG number 131323**

**2014 International utilisation**

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<tr>
<th>Country</th>
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2014 Evidence and Policy

2014 Safety and effectiveness

The original technology brief assessed the use of the InteguSeal® microbial sealant (Kimberly-Clark Worldwide, Inc., Georgia, USA) in patients undergoing coronary artery bypass graft (CABG) surgery. However, the literature search undertaken for this update did not identify any further studies on the use of InteguSeal® in this patient group. Consequently, studies published after 2011 that assessed the safety or effectiveness of the sealant in patients undergoing any cardiac surgery were considered for inclusion.

Two clinical trials were included: one randomised controlled trial (RCT) (level II interventional evidence) and one pseudo-randomised controlled trial (level III-1 interventional evidence). A recent Cochrane review, which assessed the effects of preoperative application of InteguSeal® on the rate of surgical site infections (SSIs) in patients undergoing any clean surgery, is briefly noted under ‘2014 Other Issues’. The updated search also identified studies which assessed InteguSeal® in patients undergoing oncology surgical procedures, arthroplasty and scoliosis correction. A Swedish study compared the technology to bare skin following saphenous vein harvesting in CABG surgery; however, bare skin is not considered an appropriate comparator for the sealant. None of these four studies were included in the current update.

Hanedan et al 2014

This prospective RCT enrolled patients undergoing CABG surgery, cardiac valve surgery or procedures to correct congenital cardiac anomalies. Between January 2009 and March 2010 a single site in Turkey compared InteguSeal® with standard iodine cleaning plus plain adhesive draping. Patients were excluded who had infections; skin lesions at the surgical site; a body mass index over 35 kg/m²; an anaesthetic risk score greater than 3; medical emergencies; previous cardiac surgery; or patients who required postoperative surgical exploration. All 102 patients enrolled in the study received standard perioperative care and all operative procedures were performed by the same surgical group. Hair removal was routine practice. All patients received antimicrobial prophylaxis before the first incision and when all chest tubes were withdrawn. Povidone-iodine, 10%, was applied to the surgical field for all patients and allowed to dry. Patients were then randomly assigned to receive the microbial sealant or the standard plain adhesive drape. The authors did not report the method of randomisation used and whether the outcome assessors or patients were blinded to allocation. Preoperative characteristics of the microbial sealant group (n=68) and the standard plain adhesive drape group (n=28) were comparable (Table 1).

The mean operation time was significantly longer for patients in the adhesive drape group (210 minutes) than for patients in the microbial sealant group (178 minutes; p=0.04). The reason for this was not reported. Patients were followed up for six months. Events of sternal...
wound infection, mediastinitis and mortalities were recorded. Skin cultures were obtained using a cotton swab from the skin adjacent to the incision before the planned incision (baseline), immediately prior to sternal wiring and after closure of the wound. White blood cell (WBC) and neutrophil counts, and neutrophil granulocyte percentages, were obtained pre-operatively and on the first, second, third and fifth post-operative days.

Table 1  Pre-operative and intraoperative patient characteristics

<table>
<thead>
<tr>
<th>Features</th>
<th>InteguSeal (n=68)</th>
<th>Plain adhesive drape (n=28)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>51.3 (SD 16.52)</td>
<td>48.6 (SD 17.59)</td>
<td>0.12</td>
</tr>
<tr>
<td>Men</td>
<td>44 (65%)</td>
<td>19 (68%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>24 (35%)</td>
<td>12 (43%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19 (28%)</td>
<td>10 (36%)</td>
<td>0.45</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>13 (19%)</td>
<td>6 (21%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Preoperative white blood cell count</td>
<td>7784.4 (SD 1958.2)</td>
<td>8420.4 (SD 1731.1)</td>
<td>0.14</td>
</tr>
<tr>
<td>Preoperative neutrophil count</td>
<td>4827.7 (SD 1506.5)</td>
<td>5382.1 (SD 1409.3)</td>
<td>0.10</td>
</tr>
<tr>
<td>Preoperative neutrophil granulocyte percentage</td>
<td>61.2% (SD 7.5)</td>
<td>62.3% (SD 8.3)</td>
<td>0.45</td>
</tr>
<tr>
<td>Type of operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>47 (69%)</td>
<td>18 (64%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac valve surgery</td>
<td>16 (24%)</td>
<td>8 (29%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Congenital cardiac anomaly surgery</td>
<td>5 (7%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>Length of operation (minutes)</td>
<td>178.1 (SD 63.64)</td>
<td>209.64 (SD 79.29)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Table notes: SD = standard deviation

Safety

No deaths were reported in the microbial sealant group. One of the two patients who underwent surgery for a congenital cardiac condition in the comparator group died on the second postoperative day. Two patients initially assigned to the sealant group experienced major bleeding. The surgical sites of another four patients, who were initially assigned to the control group, were found to be contaminated with bacteria (based on skin cultures taken before the incision). All six patients were excluded from the study. While the authors did not explicitly state the reasons for these events, they were not considered to be related to the sealant or adhesive drape.

Effectiveness

There was no statistically significant difference in microorganism contamination between the microbial sealant and the plain adhesive drape groups. Twenty-seven patients (40%) from the sealant group and 11 patients (39%) from the adhesive drape group were contaminated with microorganisms (p=0.97). Methicillin-sensitive coagulase-negative Staphylococcus was identified in 35 of these patients (92%) while the remaining three patients’ wounds were contaminated with Staphylococcus aureus, Staphylococcus epidermidis or Acinetobacter baumanii. Mean WBC and neutrophil counts, and neutrophil granulocyte percentages, were not significantly different between the groups at any stage.
during early follow-up. In general, these values rose from the first to the third postoperative day and returned to normal levels by the fifth day.

Waldow et al 2012

This single-centre German study evaluated the prophylactic effects of InteguSeal on the incidence of postoperative SSI after elective cardiac surgery. Between October 2010 and April 2011 a total of 998 consecutive patients underwent cardiac surgical procedures with median sternotomy. The patients were prospectively divided into two registries by alternating the administration of InteguSeal® to every second day of surgery, regardless of the surgeon’s preference. InteguSeal®, in addition to the standard preoperative skin preparation, was received by 496 patients, while the remaining 502 patients received standard skin preparation without InteguSeal®. Standard skin preparation included hair removal and application of a chlorhexidine-free alcohol-based antiseptic solution on the skin surface prior to incision, as per institutional hygiene standards. Preoperative and intraoperative patient characteristics were similar between the two groups (Table 2 and Table 3). The authors did not state whether patients with infections or skin lesions on the surgical site were excluded, however the two treatment groups had a similar overall score for probability of infection.

A total of 15 patients were excluded from the study due to death or discharge to another hospital within the first four postoperative days. Of the remaining patients, 488 patients from the InteguSeal® group and 495 patients from the comparator group were eligible for per-protocol analysis and had a follow-up period of 30 days.

Table 2  Pre-operative patient characteristics Waldow et al 2012

<table>
<thead>
<tr>
<th>Features</th>
<th>InteguSeal (n=496)</th>
<th>Non-InteguSeal (n=502)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>67.8 (SD 10.3)</td>
<td>68.1 (SD 10.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Men</td>
<td>375 (76%)</td>
<td>357 (71.1%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Mean body mass index (kg/m²)</td>
<td>28.0 (SD 4.5)</td>
<td>27.9 (SD 4.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>317 (64%)</td>
<td>300 (60%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Hypertension</td>
<td>456 (92%)</td>
<td>460 (92%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Peripheral arteriosclerosis</td>
<td>437 (88%)</td>
<td>434 (86%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Lung disease</td>
<td>342 (69%)</td>
<td>356 (71%)</td>
<td>0.71</td>
</tr>
<tr>
<td>Preoperative anticoagulation</td>
<td>364 (73%)</td>
<td>371 (73%)</td>
<td>0.93</td>
</tr>
<tr>
<td>Probability of infection (score points)</td>
<td>3.3% (10.6, SD 2.7)</td>
<td>3.3% (10.7, SD 2.6)</td>
<td>0.70</td>
</tr>
</tbody>
</table>

Table notes: SD= standard deviation
### Table 3  Intraoperative patient characteristics Waldow et al 2012

<table>
<thead>
<tr>
<th>Features</th>
<th>InteguSeal (n=496)</th>
<th>Non-InteguSeal (n=502)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of operation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>254 (51%)</td>
<td>264 (53%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Valve surgery</td>
<td>156 (32%)</td>
<td>152 (30%)</td>
<td></td>
</tr>
<tr>
<td>CABG + valve surgery</td>
<td>60 (12%)</td>
<td>60 (12%)</td>
<td></td>
</tr>
<tr>
<td>Tumour resection</td>
<td>5 (1%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td>Aortic resection</td>
<td>8 (2%)</td>
<td>7 (1%)</td>
<td></td>
</tr>
<tr>
<td>Aortic + valve surgery</td>
<td>9 (2%)</td>
<td>13 (3%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (1%)</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean duration of cardiopulmonary bypass (minutes)</strong></td>
<td>66.6 (SD 37.1)</td>
<td>71.5 (SD 49.5)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Mean cross-clamp time (minutes)</strong></td>
<td>43.9 (SD 24.0)</td>
<td>46.8 (SD 32.1)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Mean total operation time (minutes)</strong></td>
<td>147.1 (SD 44.2)</td>
<td>151.9 (SD 57.5)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Table notes: CABG = coronary artery bypass grafting; SD = standard deviation

### Safety

None of the adverse events reported were directly caused by the application of InteguSeal® or the standard skin preparation.

### Effectiveness

The incidence of postoperative mediastinitis (InteguSeal group: 2%; comparator group: 3%), or any form of SSI including mediastinitis (InteguSeal group: 11%; comparator group: 12%) was similar in both treatment groups. Of the 57 patients in the comparator group who were diagnosed with any form of SSI, two died within 30 days due to sepsis triggered by SSI. Antibiotics were necessary in 14 of the 53 patients (26%) who experienced an SSI in the sealant group and in 15 of the 57 patients (26%) who experienced an SSI in the comparator group.

A comparison of the baseline characteristics of the 110 patients who experienced any SSI and the 873 who did not experience an SSI suggested that obesity, diabetes and chronic lung diseases were linked with higher rates of SSI. Intraoperative risk factors for SSI included longer operating times, chest tubes that remained for over 24 hours and inotropic support for longer than 16 hours. The most common pathogen in infected wound cultures was *S. epidermidis*.

### 2014 Economic evaluation

No cost-effectiveness studies of InteguSeal® in cardiac surgery were identified in the literature.

### 2014 Ongoing research

No new trials have been registered with AustralianClinicalTrials.gov.au or ClinicalTrials.gov.
One ongoing trial (NCT0094979) referenced in the original technology brief had been terminated due to insufficient results and futility. This trial was an industry-sponsored, single-blind (patient) RCT investigating the use of InteguSeal® in arterial bypass surgery on lower extremities. The status of the large RCT comparing InteguSeal® to iodine and isopropyl alcohol Duraprep® (3M, St. Paul, Minnesota, USA) in oncologic surgery is currently unknown (NCT01110772).

**2014 Other issues**

A Cochrane Review by Lipp et al assessed the use of preoperative application of microbial sealants, compared with no sealant, on the rate of SSI in patients undergoing clean surgery. Three RCTs met predetermined inclusion criteria, two of which assessed patients undergoing CABG surgery and were included in the original technology brief. The third study evaluated patients undergoing elective open inguinal hernia repair. Two of the three studies included in the Cochrane review were funded by the manufacturer. Pooled results of the three RCTs found fewer SSIs following use of the sealant (10 SSIs in 261 patients, 4%) compared to no sealant (29 SSIs in 274 patients, 11%) (RR 0.36, 95% CI [0.18, 0.72]). However, given the small number of participants and included studies, and poor study quality, the authors were unable to conclude whether the sealant reduced the risk of SSI, or make any conclusions with regard to its safety.

Waldow et al (2012) was supported by Kimberly-Clark Worldwide, Inc., which provided investigators and products for the study. No potential conflicts of interest were declared by Hanedan et al (2013).

Similar products to InteguSeal, for example FloraSeal™ (Adhezion Biomedical, Wyomissing, Pennsylvania, USA) have been approved by the US Food and Drug Administration for use after topical operative skin preparations, with standard surgical draping, and prior to a surgical incision, to reduce the risk of contamination by skin flora.

**2014 Summary of findings**

The application of InteguSeal® in combination with standard preoperative practice appears to be safe, with no adverse events related to the technology. However, the included studies failed to show a statistically significant reduction in SSI when InteguSeal was compared with standard preoperative skin preparation in cardiac surgery. Further well designed RCTs are recommended to determine the effectiveness and cost-effectiveness of InteguSeal.

**2014 HealthPACT assessment**

InteguSeal® to reduce surgical site infections following coronary artery bypass graft was first assessed by HealthPACT in 2012 and was considered a technology that was likely to diffuse rapidly within Australia and New Zealand. Since that initial assessment there has been no high-quality evidence published. Therefore it is recommended that this brief be
Microbial sealant to reduce surgical site infections following cardiac surgery update: November 2014

Disseminated throughout the jurisdictions and that no further research on behalf of HealthPACT is warranted at this time.

2014 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 website.

Total number of studies 2
Total number of Level II studies 1
Total number of Level III-1 studies 1

2014 References

Microbial sealant to reduce surgical site infections following cardiac surgery

TECHNOLOGY BRIEF 2012

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  ☑ Established
☐ Experimental  ☐ Established but changed indication or modification of technique
☐ Investigational  ☐ Should be taken out of use
☐ Nearly established

Australian Therapeutic Goods Administration approval

☑ Yes  ARTG number 131323
☐ No
☐ Not applicable

International utilisation

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<tr>
<th>Country</th>
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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 preoperative treatments for cardiac surgery indications.¹

**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 septicaemia.²⁻³ SSIs occur within 30 days of surgery and manifest as pus, or swab with >10⁶ colony forming units (CFU) per mm³ 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

A strategy to reduce the incidence of SSIs is the minimisation of bacterial contamination at the surgical site. Standard practice involves patient skin preparation with an appropriate antiseptic agent. While effective preparation can reduce skin bacterial counts by 80 per cent, some organisms persist.⁴ Administration of prophylactic antibiotics has additionally reduced postoperative infection rates; however, increased use of antibiotics can result in the emergence of antibiotic-resistant pathogens.²

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Description</th>
<th>Risk of SSI</th>
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</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 viscera. (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>


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.\textsuperscript{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 outer most layer of the epidermis, the cyanoacrylates polymerise into long chains and form a solid film. Upon application, InteguSeal\textsuperscript{®} 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.\textsuperscript{3, 9, 10} In its polymerised form, InteguSeal\textsuperscript{®} is able to seal micro-abrasions on the skin and can prevent potential pathogen recolonisation.\textsuperscript{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.\textsuperscript{3} Due to the properties of InteguSeal\textsuperscript{®}, the technology can be used without further encouraging the development of bacterial resistance.\textsuperscript{6} InteguSeal\textsuperscript{®} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{12} Victorian SSI monitoring data has estimated the crude mortality rate for patients with an SSI at five per cent.\textsuperscript{13}

**Diffusion of technology in Australia**

InteguSeal\textsuperscript{®} was registered with the TGA in September 2006.\textsuperscript{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).\textsuperscript{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.\(^\text{1,15}\)

**von Eckardstein et al (2011)**\(^\text{15}\)

**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%).

Iyer et al 2011

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.\(^{13}\) The costs associated with patients who require readmission are additionally higher.\(^{1}\)

InteguSeal® 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.\(^{1}\)

**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),\(^{15}\) was sponsored by the manufacturer. No conflicts-of-interest were declared by Iyer et al (2011).\(^{1}\)

Side-effects of the sealant are rare, but can include allergic reaction or skin irritation.\(^{5}\) 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® 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. 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®, 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://tinyurl.com/99kkraa](http://tinyurl.com/99kkraa).

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<td>Total number of level II studies</td>
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**References**


**Search criteria to be used**

Microbial sealant

InteguSeal®

Surgical site infection