The use of a surgical sealant (CoSeal®) in cardiac and vascular reconstructive surgery:
an economic analysis

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Aim. We designed a study to estimate the economic impact of CoSeal® Surgical Sealant for the prevention of anastomotic bleeding in cardiac and vascular surgery. We also explored the potential economic value of CoSeal® as a means of inhibiting the formation of pericardial tissue adhesions.

Methods. A Delphi panel of 6 expert vascular and cardiac surgeons provided the assumptions and estimates needed to develop a decision analysis model to assess the impact of sealant on the costs associated with low- and high-risk forms of cardiac (valve replacement/reconstruction) and vascular (abdominal aortic aneurysm [AAA] repair, femoral bypass grafting) surgery. The primary outcome was incremental cost per patient.

Results. For valve repair/replacement surgery, sealant was expected to confer cost-savings in high-risk but not low-risk procedures. Predicted cost savings for high-risk AAA repairs were substantial, but minimal in the overall AAA group. Cost-savings were predicted for sealant use in all femoral-popliteal ePTFE bypass grafts, but in high-risk femoral-femoral ePTFE bypass grafts only.

Conclusion. According to our decision analysis model, routine use of surgical sealant in select subgroups may confer considerable economic benefits to health service budgets. Future research should aim at testing this model in a real-world hospital setting. Assessment of the value of CoSeal® in the prevention of postsurgical adhesions showed that expert surgeons see a need for effective prophylaxis. Further research into the clinical and economic benefit of this intervention is required.

KEY WORDS: Surgical sealant - Vascular surgical procedures - Cardiac surgery - Haemostasis - Adhesions.

Each year, hundreds of thousands of patients undergo cardiac and vascular reconstructive surgery. Over the last decade, improvements in surgical techniques, equipment and products have made a significant contribution to reducing the intraoperative and postoperative complications associated with these forms of surgery, and their attendant costs. However, 2 related complications that have been only partially addressed by the recent advances are: 1) protracted bleeding at the anastomotic site, and 2) the development of pericardial adhesions following cardiac surgery.

Anastomotic suture hole bleeding can increase operative blood loss, the need for transfusions and operating time. Indeed, in certain types of cardiovascular surgery, e.g. aortic aneurysm repair, it has been shown that intraoperative bleeding is associated with severe postoperative morbidity, longer hospital stays, reoperations and death.1-3 Also, adhesion formation following surgery is a problem affecting many types of surgery. For the cardiac surgeon, the development of adhesions following primary median sternotomy presents a major difficulty upon sternal re-entry. Adhesions obscure the surgeon’s view, potentially leading to injuries of the heart and the great vessels, and significantly increasing surgery time.4-6 Clearly, both complications may impose a high cost-burden on healthcare budgets.
Table I.— Results of the vascular and cardiac surgery panels’ interviews (3 rounds) for each type of surgery. Mean (range) values are given for each variable, based on a hypothetical cohort of 100 patients.

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<tr>
<td></td>
<td>High-risk</td>
<td>Low-risk</td>
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<td></td>
<td>67% (20-80%)</td>
<td>53% (20-50%)</td>
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<td></td>
<td>87% (70-100%)</td>
<td>87% (70-100%)</td>
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<tr>
<td></td>
<td>Nonresponders</td>
<td>Responders</td>
<td>Nonresponders</td>
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<tr>
<td>AAA repair</td>
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<td></td>
<td></td>
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<tr>
<td>Total surgery time per patient (min)</td>
<td>180 (180-180)</td>
<td>–</td>
<td>160 (140-180)</td>
</tr>
<tr>
<td>Bleeding timea (min)</td>
<td>30 (17-45)</td>
<td>13 (10-15)</td>
<td>23 (10-30)</td>
</tr>
<tr>
<td>Patients requiring blood transfusion, %</td>
<td>36 (30-40)</td>
<td>21 (20-23)</td>
<td>21 (3-30)</td>
</tr>
<tr>
<td>No. of blood units required per patient</td>
<td>2.3 (2-3)</td>
<td>1.7 (1-3)</td>
<td>1.7 (1-3)</td>
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<tr>
<td>Patients needing haemostatic agents, %</td>
<td>46 (8-80)</td>
<td>38 (5-70)</td>
<td>43 (8-70)</td>
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<tr>
<td>No. of haemostatic agents needed per patient</td>
<td>3.7 (2-6)</td>
<td>3.3 (1-6)</td>
<td>3.3 (1-6)</td>
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<tr>
<td>Valve replacement/reconstruction</td>
<td></td>
<td></td>
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<tr>
<td>Total surgery time per patient (min)</td>
<td>238 (233-240)</td>
<td>–</td>
<td>157 (140-180)</td>
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<tr>
<td>Bleeding timea (min)</td>
<td>55 (34-60)</td>
<td>21 (13-30)</td>
<td>25 (15-35)</td>
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<tr>
<td>Patients requiring blood transfusion, %</td>
<td>53 (28-70)</td>
<td>31 (14-50)</td>
<td>30 (15-45)</td>
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<tr>
<td>No. of blood units required per patient</td>
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<tr>
<td>Patients needing haemostatic agents, %</td>
<td>34 (2-60)</td>
<td>15 (0-30)</td>
<td>17 (0-40)</td>
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<tr>
<td>No. of haemostatic agents needed per patient</td>
<td>2 (1-3)</td>
<td>1.3 (0-2)</td>
<td>0.7 (0-1)</td>
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<tr>
<td>Fem-fem ePTFE</td>
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<tr>
<td>Total surgery time per patient (min)</td>
<td>110 (60-150)</td>
<td>–</td>
<td>73 (60-100)</td>
</tr>
<tr>
<td>Bleeding timea (min)</td>
<td>32 (20-45)</td>
<td>13 (8-20)</td>
<td>22 (15-30)</td>
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<tr>
<td>Patients requiring blood transfusion, %</td>
<td>2 (0-3)</td>
<td>1 (0-2)</td>
<td>1 (0-2)</td>
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<tr>
<td>No. of blood units required per patient</td>
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<td>0.7 (0-1)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td>Patients needing haemostatic agents, %</td>
<td>47 (1-100)</td>
<td>17 (0-30)</td>
<td>23 (0-50)</td>
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<tr>
<td>No. of haemostatic agents needed per patient</td>
<td>2 (1-3)</td>
<td>1.7 (0-3)</td>
<td>1 (0-2)</td>
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<tr>
<td>Fem-fem PF/autologous</td>
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<tr>
<td>Total surgery time per patient (min)</td>
<td>97 (60-140)</td>
<td>–</td>
<td>73 (60-100)</td>
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<tr>
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<td>17 (10-30)</td>
<td>8 (5-10)</td>
<td>13 (8-20)</td>
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<tr>
<td>Patients requiring blood transfusion, %</td>
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<td>1 (0-2)</td>
<td>1 (0-2)</td>
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<tr>
<td>No. of blood units required per patient</td>
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<td>0.7 (0-1)</td>
<td>1 (0-2)</td>
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<tr>
<td>Patients needing haemostatic agents, %</td>
<td>44 (1-100)</td>
<td>15 (0-30)</td>
<td>23 (0-50)</td>
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<tr>
<td>No. of haemostatic agents needed per patient</td>
<td>2 (1-3)</td>
<td>1.7 (0-3)</td>
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(To be continued)
The use of surgical sealants to control anastomotic bleeding has been widely adopted in cardiac and vascular surgery. Recent research indicates that these agents may also have a role in the inhibition of postsurgical adhesion formation, given that both problems result from a lack of tissue sealing.

Based on the results of 2 randomized controlled trials, a sprayable polymeric matrix, CoSeal® Surgical Sealant (Angiotech Biomaterials Corp, Palo Alto, CA, USA; manufactured and distributed by Baxter Healthcare, Deerfield, IL, USA) has been approved in the USA, Europe and Canada, for use in sealing suture lines along arterial and venous reconstructions.

In Europe and Australia, CoSeal® is also approved for use in patients undergoing cardiac surgery to prevent or reduce the incidence, severity and extent of postsurgical adhesion formation. This indication was based on the findings of a study of infants undergoing staged surgical correction for congenital heart abnormalities, and earlier preclinical research. However, there is a pressing need to evaluate the utility of CoSeal® for preventing adhesions in adult patients requiring resternotomy. Ten percent to 20% of coronary artery bypass graft (CABG) or valve replacement patients are expected to undergo another cardiac procedure within 10 years, and at least 3% are expected to experience serious haemorrhage as a consequence. There is no treatment for existing lesions, so prevention is key.

In spite of the increase of clinical data to support the efficacy of CoSeal® in the prevention of anastomotic bleeding and the inhibition of adhesion formation, the important question of cost-effectiveness remains unanswered. Consequently, the main aim of our study was to estimate the economic impact of prophylactic CoSeal® use for the prevention of anastomotic bleeding in vascular and cardiac reconstructive surgery. The secondary aim was to explore the potential economic value of CoSeal® as a means of preventing the formation of adhesions following cardiac procedures requiring sternal entry.
Materials and methods

Delphi panels

In the absence of any published analyses on the cost implications of surgical sealant use, the Delphi technique was used to derive the core assumptions and estimates needed to develop a decision analysis model for the economic evaluation of sealant use in the prevention of bleeding. In addition, the technique was used to explore the potential economic value of CoSeal® in the prevention of adhesion formation.

Developed in the 1950s, the Delphi technique is designed to aid decision-making or forecasting in situations where there is a lack of historic, economic or technical data, which calls for some form of human judgement. It is regarded as a procedure to “obtain the most reliable consensus of a group of experts.” This consensus is achieved by administering a series of intensive questionnaires to each group member, interspersed with controlled opinion feedback, until group agreement is reached. The Delphi technique is characterised by 4 key features - anonymity, iteration, controlled feedback, and the statistical aggregation of group response.

Six highly-experienced surgeons were recruited - 2 specialized in vascular surgery, 3 in cardiac surgery, and 1 was skilled in both forms of surgery. According to specialty, we formed 2 panels - a vascular surgery panel (n = 3), and a cardiac surgery panel (n = 4). To ensure an international perspective, panel members were drawn from France, Italy, Spain, Germany, Belgium and the Netherlands.

Primary objective - use of sealant to prevent bleeding in cardiac and vascular reconstructive surgery

Panel members participated in 3 rounds of interviews: 1) an exploratory interview; 2) a data collection interview; and 3) a consensus interview. After each round of interviews, members were asked to consider and explain their responses by a process of controlled feedback. Subsequently, participants were pre-
sented with the group’s aggregated answers and the anonymous responses of individual members, and were asked to comment on these. This structured approach eventually led to the derivation of the core variables needed for the decision analysis model. The anonymity of participants was maintained until the end of the project.

In keeping with the approved indications of CoSeal®, the exploratory round of interviews focused on: 1) two cardiac procedures - coronary artery bypass graft (CABG) and valve replacement/reconstruction; and 2) four vascular procedures - abdominal aortic aneurysm (AAA) repair, carotid artery repair, femorofemoral (fem-fem) bypass graft, and femoral-popliteal (fem-pop) bypass graft. Surgeons were questioned about their experience with these procedures and their expectations regarding the utility of a sealant to reduce intraoperative bleeding in each of the surgical settings chosen. This enabled us to distinguish between low- and high-risk scenarios for each type of operation, and to determine meaningful clinical and economic measures for use in the model.

The second round of interviews focused on collecting baseline information on the clinical and economic variables selected in round one, and predicting the effect of sealant use on these variables for each of the chosen procedures. By extension, other measures to reflect the anticipated effects of sealant use were developed. These included reduction in operating time; reduction in bleeding time (defined as time taken for the anastomotic site to dry); reduction in number and volume of transfusions required; and reduction in the use of haemostatic agents. The third round of interviews was used to reach consensus on the estimates and assumptions developed.

**Decision analysis model**

The estimates and assumptions derived during the interview process were used to develop a simple decision analysis model, created with Microsoft® Excel®, to project the impact of sealant use in selected surgical settings in a hypothetical cohort of 100 patients. The model distinguished between high- and low-risk patients and, in case of sealant use, between responders and nonresponders. Responders were defined as patients in whom the use of sealant would lead to a decrease in operating time, bleeding time and need for transfusions.
for blood-products. Nonresponders were assumed to experience a course similar to that of a typical patient who does not receive sealant. The model relates only to the perioperative period and, therefore, it was not necessary to discount the costs or the effects in the decision analysis model.

The primary outcome of the model was incremental cost per patient. A probabilistic sensitivity analysis was performed to assess the robustness of the modeled results to within reasonable variation for clinical and economic variables. This used minimum and maximum values as reported by the panels for each variable, and a range of ±5 € for cost per minute operating time. Sensitivity analyses were performed using @Risk® software (Palisade, Europe), for high-risk, low-risk and total populations.

Secondary objective - exploration of possible use of sealant to reduce adhesions in cardiac redo surgery

We used our cardiac surgery panel to explore the potential economic impact of CoSeal® as a means of reducing or preventing the formation of adhesions common in repeat cardiac surgery. As for the primary study, participants completed 3 rounds of interviews.

Results

Use of sealant to prevent bleeding in cardiac and vascular reconstructive surgery

DELPHI PANELS

The first round of interviews showed that the expert panels considered the use of a surgical sealant to have potential value in valve replacement/reconstruction, AAA repair, and fem-fem and fem-pop bypass grafting. In contrast, the use of surgical sealant in CABG and carotid artery repair was not expected to be as beneficial, so these forms of surgery were not included in the analysis. Key clinical outcomes considered to be relevant to a cost-effectiveness assessment included bleeding time, operating time and the use of blood transfusions. Fatal complications were not included because they were not considered preventable by use of a sealant.
High-risk scenarios were determined by the panels, and all non-high-risk scenarios were classed as low-risk. High-risk was defined as an increased risk of bleeding in specific patient groups or related to specific surgical techniques. This varied across the different types of cardiac and vascular surgeries studied in our analysis. However, for all procedures, calcified arteries or anaemia were considered to be high-risk conditions. Additional high-risk scenarios for valve replacement or reconstruction included use of a large body vessel or pulmonary autograft; length of stitches and suture line; advanced age or reoperation at the same site. Additional high-risk criteria in AAA repair included very thin aorta walls and very large aneurysms. In fem-fem and fem-pop bypass graft procedures, the use of expanded polytetrafluoroethylene (ePTFE, i.e. Gore-Tex®) was considered to be a high-risk factor.

Overall, the panels estimated that for AAA repair, 67% of procedures would be classed as high-risk; for valve surgery, 43% of operations would fall under this classification, and for femoral grafts, approximately 23%. The high-risk surgeries were expected to benefit more from use of a sealant than lower-risk forms of surgery.

Table I shows the cardiac and vascular surgery panels’ results for each type of surgery. The procedure considered to carry the highest risk of intraoperative bleeding was AAA repair, with 67% of procedures classed as high-risk. However, the greatest reductions in bleeding time and operating time as a consequence of sealant use were expected in valve replacements/reconstructions. Regarding the estimates of operating time for valve replacements/reconstructions, valve failure may extend operating times to up to 8 h. As this event is not common, it was not factored into the estimates of average operating time for valve surgery. For femoral graft surgery, bleeding time was expected to be longer with the use of ePTFE grafts compared with venous grafts and polyester fibre (PF) grafts (i.e. Dacron®).

The costs used in the model were derived from the Delphi panel interviews and other sources, and are listed in the footnote of Table II.16

**DECISION ANALYSIS MODEL**

The estimates derived from the Delphi panels were entered into the decision analysis model to calculate the differences in cost between routine prophylactic use of a surgical sealant and not using a sealant for each of the chosen procedures in high-risk, low-risk, or all scenarios (Figure 1).

**ABDOMINAL AORTIC ANEURYSM REPAIR**

To understand how the model works, refer to Table II, which shows results of the AAA repair analysis, by way of example. In this scenario, the model predicted that routine use of a topical sealant in high-risk AAA surgery would lead to cost savings of 134 € per patient compared to no sealant. Because of the reduced surgery time and the lower costs per patient, this intervention is classed as a dominant strategy (defined as an intervention that combines cost benefits with neutral or positive effects when compared to the control intervention, i.e. use of surgical sealant versus no use of sealant). In the case of a low-risk AAA repair, the routine use of sealant was estimated to cost 214 € per patient. As shown in the last column of Table II, by combining the net costs of sealant use in high- and low-risk patient groups we derived an incremental value that reflects the use in the whole population, regardless of risk stratification. This total incremental analysis indicates that for valve repair operations as a whole, routine use of sealant is expected to decrease costs by 18 € per patient and to decrease bleeding time by 13 min per patient. By extrapolating the estimates seen for sealant use in the total AAA repair population, it is expected that sealant use may reduce the proportion of patients requiring a blood transfusion by as much as 38%.

**VALVE REPLACEMENT/RECONSTRUCTION**

Similar results were obtained for high-risk valve replacement/reconstruction surgery, with a predicted cost saving of 222 € per patient compared to no sealant use (Table III). In contrast to the AAA surgery results, the total incremental analysis indicated that for valve repair operations as a whole, routine use of sealant is expected to increase costs by 219 € per patient but decrease bleeding time by 12 min per patient (data not shown). Sealant use may also reduce the proportion of patients requiring a blood transfusion by as much as 18%.

**FEM-FEM AND FEM-POP BYPASS GRAPHS**

As femoral bypass procedures using ePTFE carry a considerable risk of haemorrhage,17-19 we were not surprised to see our model indicate that use of sealant
would be a dominant strategy for high-risk fem-fem ePTFE grafts and for all fem-pop ePTFE grafts (Table III). For other types of graft material (principally PF), the use of sealant did not appear to be beneficial in any patient subset, as expected.

SENSITIVITY ANALYSIS

The data from the third round interviews (the consensus round) was used for the base case scenario and the individual estimates from experts collected in the second interview round were used in the sensitivity analysis. The univariate sensitivity analysis revealed that for all procedures except valve replacement/reconstruction, the most important variable was the estimate of bleeding time in the control group, followed by cost per minute of operating time and responsiveness to sealant. This was the case for both the high-risk populations and the total populations for each type of surgery other than valve surgery.

For the high-risk valve surgery population, the most important variable was responsiveness to sealant, followed by bleeding time in the control group and costs per minute operating time. For the total valve surgery population, the most important variable was also responsiveness to sealant, followed by the proportion of population classed as high-risk, and bleeding time in the control group.

With respect to all procedures, the widest range of individual estimates was related to the use of haemostatic agents which ranged between 1% and 100% for the high-risk interventions and between 0% and 50% in the low-risk interventions. However, univariate sensitivity analysis revealed that haemostatic agents had a very limited impact on the costs per patient. Table III includes the results from the probabilistic sensitivity analysis.

Exploration of possible use of sealant to reduce adhesions in cardiac redo surgery

The cardiac surgery panel indicated that the groups most likely to benefit from prevention or reduction of adhesion formation following cardiac surgery were infants undergoing staged surgical repair for congenital heart disease, and adults undergoing CABG or valve replacement/reconstruction. They estimated that approximately 15% of patients undergoing a CABG and 10% of patients undergoing valve surgery would require a reoperation within 10 years.

Whereas the panel members did not rank the type or location of thoracic adhesions as being important factors, they agreed that the presence of adhesions requiring sharp dissection posed a difficulty for the surgeon and was likely to increase the risk of cardiac injury and lengthen operating time. Consequently, reduction in operating time may be considered as a variable for future economic evaluations of the use of a sealant to inhibit adhesion formation. Such an evaluation would also take into account the smaller quantity of sealant required for adhesion prevention compared with bleeding prevention.

The panel also agreed that redo operations that occur within a short timeframe increase the need for sharp dissection. Consequently, the economic value of sealants to reduce adhesion formation was predicted to be greatest in staged repair of congenital heart disease and in adults at risk of short-term reoperation, e.g. certain types of valve repair.

Discussion

In the absence of published data from clinical studies, we found the Delphi technique to be an effective way of working out the key variables and core estimates and assumptions required to develop a decision analysis model that simulates the economic impact of surgical sealant use in predefined settings.

The resulting model indicated that routine use of sealant is expected to yield cost savings for high-risk AAA repairs, i.e. routine sealant use appeared to be a dominant strategy in this indication. Moreover, despite the fact that for low-risk AAA patients routine sealant use might be considered a poor investment of resources, overall, a limited cost benefit remained in the total AAA population. In high-risk valve repair surgeries, all fem-pop ePTFE bypass grafts, and high-risk fem-fem ePTFE bypass grafts, routine sealant use also appeared to be the dominant strategy. Conversely, there were no predicted cost savings associated with the use of sealants in the total valve surgery or total fem-fem ePTFE bypass graft populations, or in any of the PF graft groups. The higher risk of bleeding associated with ePTFE relative to PF translated into greater cost savings for sealant use in these subgroups.

Sensitivity analyses indicated that overall, the model was most sensitive to changes in estimated bleeding time in the control (nonsealant) group, and in the estimated cost per minute operating time. Conse-
quently, these variables would benefit from further study.

Although some of our cost estimate parameters were specific to the Netherlands, *e.g.* cost per minute operating time, others were derived with the input of our international panels based on their collective clinical experience. Given that our panels comprised surgeons from 6 European nations, all of whom described very similar approaches to the operative procedures assessed, we believe that the findings can be tentatively extrapolated to other European settings.

In the absence of published data on the cost-effectiveness of surgical sealant, this model is designed to estimate potential cost-savings that may be derived from the use of sealant in cardiac and vascular reconstructive surgery. Based on these preliminary analyses, routine use of sealant in certain types of surgery is predicted to confer not only cost-savings, but also favourable outcomes such as reduced bleeding time, reduced operating time and the reduced need for transfusions. For example, use of sealant in femoral ePTFE bypass grafting was predicted to reduce both bleeding time and operating time by 14 min.

With AAA repair ranked by our expert panels as the surgery associated with the highest risk of intraoperative bleeding, it is not surprising that the projected reduction in the need for transfusions was most marked in this group, with 38% fewer high-risk patients expected to require transfusion when sealant is used *versus* no sealant. This translates into a predicted saving of 35.5 U of blood per 100 patients (from an estimated 70 U needed when no sealant is used, with a concomitant reduction in the use of haemostatic agents conferring additional benefit in terms of cost savings) (data not shown).

Our preliminary assessment of the economic value of CoSeal® in the prevention of postsurgical adhesions showed that expert surgeons see a need for effective prophylaxis to help decrease the need for sharp dissections, minimize the risk of injury, and reduce operating time. The case for sealant use in the staged repair of congenital heart defects as exemplified by Konertz *et al.* is convincing, although further studies are needed to confirm this approach in paediatric surgery. In adult cardiac surgery, however, the key determinant influencing the economic value of prophylactic CoSeal® use will be the ability to assess which patients are at risk of short-term redo. For example, for patients undergoing valve replacements, risk factors for reoperation include a history of endocarditis, the use of a small valvular prosthesis, being male, and having a mitral valve replacement. The panel’s estimates that 15% of CABG patients and 10% of patients undergoing valve surgery will require a reoperation within 10 years are in line with previous estimates.

The panel agreed that further research to explore the clinical and economic benefit of CoSeal® for the prevention of adhesions in adult and paediatric surgery is essential.

Conclusions

Based on results derived from a Delphi Panel, our decision analysis model indicates that routine use of surgical sealant in select subgroups may confer considerable economic benefits to hospital and health service budgets. Future research should aim at testing this model in a real-world hospital setting. Similarly, our preliminary assessment of surgical sealant use for the inhibition of pericardial adhesions underscores the need for further research into the clinical and economic benefit of this intervention.

References