A Cost-Effectiveness Analysis of Intraoperative Cholangiography in the Prevention of Bile Duct Injury During Laparoscopic Cholecystectomy

David R Flum, MD, MPH, Christopher Flowers, MD, MS, David L Veenstra, PharmD, PhD

BACKGROUND: Recent population-based studies have demonstrated that the use of intraoperative cholangiography (IOC) during laparoscopic cholecystectomy (LC) is associated with a decrease in the rate of common bile duct (CBD) injury. The cost implications of a management strategy involving routine IOC use have not been adequately evaluated.

STUDY DESIGN: Decision analytic models were developed to analyze costs and benefits of routine IOC use during LC. The models were used to calculate the cost per life saved, cost per CBD injury avoided, and incremental cost of IOC when used routinely. Transition probabilities, costs, and outcomes were derived from published sources. Sensitivity analyses were used to account for uncertainty in these estimates.

RESULTS: Using base-case estimates, management of patients undergoing LC with routine IOC would cost $100 more per LC. Routine IOC would prevent 2.5 deaths for every 10,000 patients at a cost of $390,000 per life saved ($13,900 per life year saved). The cost per CBD injury avoided without IOC use is $87,143. The cost per CBD injury avoided is less for procedures done in high-risk patients (approximately $8,000) or by less experienced surgeons (approximately $61,000).

CONCLUSIONS: These models describe settings where the cost of IOC and the reduction in CBD injury rates make routine IOC use cost effective. Routine IOC use among less experienced surgeons and in high-risk operations is the most cost effective, but the cost implications of routine use for the general population should also be considered cost effective. (J Am Coll Surg 2003;196:385–393. © 2003 by the American College of Surgeons)

Surgeons have long debated the routine use of intraoperative cholangiography (IOC) during laparoscopic cholecystectomy (LC). Advocates of IOC accentuate the benefits of an "operative roadmap" in reducing the frequency and severity of injuries to the CBD. Those opposed to routine IOC use have noted its increased cost and equivocal benefit. Until recently, there have been little data regarding the benefits of IOC in preventing CBD injury. Small series evaluated the use of IOC in LC but found no consistent benefit to IOC. The benefits of IOC might be difficult to demonstrate in a case series because CBD injury is an infrequent event. Two recent population-based cohort studies have clarified this issue by demonstrating reductions in the rate of CBD injuries in patients managed with IOC. Flum and colleagues studied more than 30,000 LCs performed in the state of Washington from 1991 to 1998 and found injuries to be nearly half as likely (odds ratio—0.6) when IOC was used (95% confidence interval [CI]: 0.39, 0.96). Fletcher and colleagues reviewed 7,000 LCs performed in Western Australia during the early 1990s and found a reduction close to 50%. Both reports identified situations in which the relative risk of injury increased dramatically when IOC was not used. In Washington State, surgeons who had performed fewer than 36 LCs were 2.2 times (95% CI: 1.31, 3.7) more likely to injure the CBD when IOC was not used. In Fletcher's study, cases considered complex (including those complicated by pancreatitis, cholangitis, obstruc-

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From the Robert Wood Johnson Clinical Scholar Program (Flum, Flowers), the Departments of Surgery (Flum) and Pharmacy (Veenstra), Seattle Veterans Administration Medical Center (Flowers), University of Washington, Seattle, WA.

Correspondence address: David R Flum, MD, MPH, Department of Surgery, University of Washington, Box 356410, Seattle, WA 98195-7183.
Abbreviations and Acronyms

CBD = common bile duct
CI = confidence interval
IOC = intraoperative cholangiography
LC = laparoscopic cholecystectomy

Costs associated with CBD injury were estimated to be $700, with an eight-fold increase in risk when IOC was not used.

Cost appears to be a major factor in opinions about cholangiogram use. In light of better data regarding the use of IOC in preventing CBD injury, we developed a cost-effectiveness model to evaluate the use of IOC during LC. Cost analysis of operative interventions is challenging because of cost averaging, which tends to mask the true cost of used items and widely varying operating room costs. This variability is reflected in published estimates of IOC costs. Some authors have approximated the cost of IOC at more than $700, and others have shown that an LC performed with IOC costs about $100 more than one performed without IOC at the same institution. To account for the variability in IOC costs, this study uses a modeling approach to incorporate uncertainty surrounding the cost of IOC into the decision-making process. The purpose of this study was to better inform decision-making surgeons by determining the estimated cost and likely range of costs associated with the use of IOC in the prevention of CBD injury.

**METHODS**

**Decision model**

Two decision models were developed to compare IOC use during LC to LC performed without IOC. Both models adopt the health care payer perspective to examine costs and benefits associated with IOC use. Model 1 (Fig. 1) was used to calculate the cost per life year saved. This model tracks costs and benefits during the time horizon from LC until hospital discharge, successful CBD injury repair, or death. It considers the costs downstream of CBD injury related to repair and the risk of death after injury and after repair. The possibility of postoperative death without CBD injury was not considered because this event is rare. Because death from CBD injury is also a rare event, model 2 (Fig. 2) was created to compare the cost per CBD injury avoided using routine IOC versus no IOC use. This model uses CBD injury as its endpoint and ignores events that occur after injury, avoiding counting costs associated with injury in the cost of preventing the injury. Transition probabilities, costs, and outcomes were derived from published sources and available primary data. All dollar estimates were adjusted for inflation to the year 2000.

![Figure 1. Complete model of cholangiogram use and outcomes. CBD, common bile duct.](image-url)
Table 1. Probabilities of Transition Points and Outcomes

<table>
<thead>
<tr>
<th>Transitional probabilities</th>
<th>Base-case value</th>
<th>Alternative values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of CBD injury for cases performed with IOC</td>
<td>19 per 10,000 cases</td>
<td>21/10,000 (baseline risk-all patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22/10,000 (risk-complex)</td>
</tr>
<tr>
<td>Rate of CBD injury for cases performed without IOC</td>
<td>33 per 10,000 cases</td>
<td>42/10,000 (risk-early experience)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>43/10,000 (baseline risk-all patients)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>169/10,000 (risk-complex)</td>
</tr>
<tr>
<td>Rate of reoperation</td>
<td>0.33(^a)</td>
<td>0.125(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.17(^c)</td>
</tr>
<tr>
<td>Rate of death associated with CBD injury</td>
<td>0.11(^d)</td>
<td></td>
</tr>
<tr>
<td>Rate of death after CBD repair</td>
<td>0.06(^e)</td>
<td>0.187(^f)</td>
</tr>
</tbody>
</table>

CBD, common bile duct; IOC, intraoperative cholangiogram.

**Likelihood of events**

**Rates of CBD injury**

Two recent studies demonstrate lower rates of CBD injury in patients managed with IOC. Evaluating the outcomes of more than 30,000 patients undergoing LC, Flum and associates' identified CBD injury in 39 of 19,511 LCs performed with IOC (rate of 20 injuries per 10,000 patients). Fletcher and colleagues' found a similar rate of CBD injury with IOC use (rate of 21 injuries per 10,000 patients) in a cohort of 7,000 patients who had LCs in Australia. When LCs were performed without IOC, both studies found that injury rates were notably higher. In Flum’s study, injuries occurred at a rate of 33 per 10,000 patients when LCs were performed without IOC. For surgeons who had previously performed fewer than 36 LCs, the injury rate was 42 per 10,000. Fletcher and colleagues found that CBD injury rates were as high as 169 per 10,000 when comorbid conditions, such as pancreatitis, cholangitis, obstructive jaundice, and acute cholecystitis were present. The relative risk of CBD injury for LCs performed with IOC was 0.6 (95% CI: 0.39, 0.96) in Flum’s study and 0.5 (95% CI: 0.35, 0.70) in Fletcher’s study. In high-risk patients, the relative risks of injury without IOC were 2.2 (95% CI: 1.31, 3.74) among early-experience surgeons and approximately 8.0 among patients with complex diagnoses. CBD injury rates of 19 per 10,000 patients in cases performed with IOC and 33 per 10,000 in cases performed without IOC were used in our base-case analyses (Table 1). When IOC was not used, these same studies found a rate of injury ranging from 33 to 42 per 10,000 depending on the experience of the surgeon and 27 to 169 per 10,000, based on case complexity. This range of injury rates was used in the sensitivity analyses to address the uncertainty present in the point estimates.

**Mortality rates after CBD injury**

Only clinically significant CBD injuries (those requiring operative repair of the CBD) were modeled in our analyses because these were the types of injuries considered in the estimates of relative risk in the cohort studies by Flum and colleagues. As a result, all patients who sustained CBD injuries in the model proceeded to CBD repair or death. The attributable incidence of death from CBD injury before repair is difficult to estimate. Anecdotal reports of patient death soon after LC have been noted, but ascertaining cause is difficult without autopsy confirmation. A mortality rate of 11% associated with CBD injury was noted in one medicolegal analysis. This rate comes from unpublished insurance data from the early 1990s, but the author did not identify which of these patients underwent operative repair. Eleven percent was used in the base-case analysis to estimate the cost per life year saved.

**Repair after CBD injury**

The population-based rate of successful CBD repair has not been determined. Among 42 patients with CBD injuries that progressed to litigation, an average of two operative repairs (range 1 to 8) were required. Published series report rates of reoperation for patients referred to an academic center for management. In the

![Figure 2](image_url). Simplified model of cholangiogram use and outcomes. CBD, common bile duct.
Table 2. Costs of Transition Points and Outcomes

<table>
<thead>
<tr>
<th>Costs/procedures</th>
<th>Base-case value ($)</th>
<th>Alternative values ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative cholangiography</td>
<td>1222</td>
<td>7715</td>
</tr>
<tr>
<td></td>
<td>9714</td>
<td></td>
</tr>
<tr>
<td></td>
<td>31516</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7384</td>
<td></td>
</tr>
<tr>
<td>Repair of common bile duct</td>
<td>13,612137</td>
<td>18,57417</td>
</tr>
<tr>
<td></td>
<td>30,00001,19</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100,0006</td>
<td></td>
</tr>
<tr>
<td></td>
<td>300,00065,19</td>
<td></td>
</tr>
<tr>
<td>Cost of in-hospital death after repair (estimated)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>100,000</td>
<td></td>
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</table>

largest of these series,7 reoperation was required in 21 of 63 patients (33%) who had primary end-to-end anastomoses or biliary enteric bypass. Thirty-three percent was used in our base-case, but it might overestimate the rates of reoperation seen in the community if referrals to academic medical centers occur for more complex injuries. Values ranging from 12.2%10 to 33% were included in the sensitivity analyses.

Death after CBD injury repair

Several reports5,11-14 have detailed short-term and intermediate outcomes after repair of CBD injuries. There is wide variability in reported outcomes after surgical repair. The greatest influence on outcome of the repair is the expertise of the surgeon11 and the number of attempted repairs before the definitive repair. In the largest of these reports, the mortality rate after surgery was 0% in a multicenter series of 81 referred patients11 and has ranged from 6%10 to 18.7%13 in smaller individual series. A death rate of 6% after repair was used in the base-case analysis and each of the other values was explored in one-way sensitivity analysis.

Costs

Intraoperative cholangiogram

A wide range of values for the cost of IOC has been identified in a review of the medical literature. Some researchers have speculated that IOC costs more than $700.16 To determine the cost of IOC at one institution, Traverso and associates8 performed a prospective, "micro-cost" analysis of biliary surgery and found IOC to cost $97 ($85 for radiology costs and $12 for cholangiogram-related disposables).14 In that series, total operating room costs ranged from $1,401 to $1,548, with the sum of all costs for LC being less than $2,500. Fletcher10 itemized the costs associated with IOC use and estimated the total cost of IOC to be $77. If the cost of purchasing a new, $150,000 fluoroscope is considered, the estimated cost of an IOC is projected to be $315 per use (with 100% depreciation of the fluoroscope over 5 years).16 Each of these measures suggests that the cost of IOC is less than the $700 amount previously proposed.

For our base-case (Table 2), we used the difference between average costs in Washington state of LCs performed with IOC ($8,649) and LCs without IOC ($8,527). These costs were derived using claims data on LCs performed at more than 130 hospitals in Washington state applying a standardized charge to cost ratio and inflating to year 2000 dollars. Although subject to regional variations, this estimate of IOC cost incorporates variation across practice settings and is similar in magnitude to the itemized cost estimations of cholangiography by Traverso and colleagues8 and Fletcher.11 For this analysis, we included multiple estimates of the cost of IOC, including the full range of reported values in the literature and a base-case estimate that comes from administrative data that is inclusive of CPT codes, added operating room time, and supplies. Although not specifically cited, cost estimates used in this analysis also included costs derived from professional fees based on CPT codes. The base-case uses $122 as the cost of IOC, but all other estimates of IOC cost are included in the range of values considered in the sensitivity analysis.

CBD injury repair

In a case-control study, the cost of CBD injury repair was found to be $13,612.17 This report evaluated several repair procedures and found a narrow range of costs (after applying a hospital-specific cost-to-charge ratio) with an upper limit of approximately $18,000. This is considerably lower than estimates that have been previously offered ($100,000 to $300,000).10,11,19 This lower estimate fails to account for reoperations and other procedures related to biliary stricture after repair. Because reoperation and endoscopic procedures are common occurrences after CBD repairs, this value might underestimate the total cost of repair. The $13,000 estimate was used in the base-case. Although a likely underestimate, it biases against IOC being cost effective by limiting the...
costs of repair that occur more often in the no-IOC arm of the model.

**Cost of in-hospital death after CBD injury**

No cost was assigned to death after CBD injury or repair in the base-case to avoid attributing valuing lives saved both economically and clinically (double-counting). A range of costs for end-of-life care ending in death after CBD injury was included in a sensitivity analysis, with values ranging from $0 to $100,000. Such costs might include several days in the ICU (at several thousand dollars per day) with a clinical syndrome such as sepsis.

**Outcomes assessment and sensitivity analyses**

The primary outcomes measured were cost per life saved (determined from model 1) and cost per avoided CBD injury using IOC (determined from model 2). Life expectancies for patients surviving LC were based on the proportion of women (74.4%) and men who underwent LC in the state of Washington and their average ages at the time of the LC (48.7 and 57.7 years, respectively). These data were entered into the Group Annuity Mortality 83 actuarial, mortality table to calculate age-specific life expectancies for men (22.6 years) and women (36.2 years), and the population (32.7 years). The population life expectancy was used to calculate the life years saved using the IOC strategy. A tornado diagram was constructed to assess the variables that had the greatest impact on the primary outcomes variables. One-way sensitivity analyses were conducted to evaluate the uncertainty in the model and to incorporate the full range of data from all sources. These analyses were performed by varying one parameter while holding the other fixed. Base-case values were varied in the sensitivity analyses to include all values described in the literature. These ranges were selected to attempt to include the true variability in these estimates present across a variety of health care settings.

**RESULTS**

Model 1 predicts 3.4 deaths per 10,000 LCs with IOC and 5.9 deaths per 10,000 LCs without routine cholangiography. So using routine IOC would prevent 2.5 deaths for every 10,000 patients who underwent LC. When the cost of all medical care after injury is accounted for as is the increased cost of IOC, managing 10,000 patients with IOC would cost $100 more per LC. This cost is slightly less than the $122 per IOC used as an input to the model because the strategy of managing patients without IOC incurs more downstream costs because of the increased numbers of injuries. Combining costs and effects reveals that routine use of IOC would cost more than $390,000 per life saved and approximately $13,300 per life year saved.

Because events downstream of CBD injury exert little influence on model 1, model 2 was used to calculate the cost per CBD injury avoided and assess how changes in the cost of IOC and reduction in CBD injury from IOC influence this measure. The base-case estimates in model
2 (cost of IOC, $122; attributable risk reduction in injury because of IOC, 14 in 10,000) show the cost per CBD injury avoided was $87,100. When the reduction in injury from IOC use was varied in a one-way sensitivity analysis from no difference to 150 injuries per 10,000, the cost per CBD injury avoided ranged from $8,185 to more than $150,000 (for risk reduction of less than 10 injuries per 10,000 cases) (Fig. 3). This model estimates that for surgeons who have performed fewer than 36 earlier LCs (where the absolute risk reduction with IOC is 0.2%), the cost per CBD injury avoided with IOC was $60,983. In cases considered by Fletcher to be complex, the cost per CBD injury avoided with IOC was slightly more than $8,000. These results suggest that the difference in LC cost with IOC is highly dependent on the risk reduction from IOC when viewed in the context of the CBD injuries.

Figure 4 demonstrates the impact of varying the model parameters on total costs. In the diagram, values to the left of zero indicate LC without IOC is more costly.

DISCUSSION

Although CBD injury is a complication of LC, distinguishing between LC and IOC to determine whose cost would be attributable to IOC would be difficult. Desper et al have compiled a list of complications related to IOC, which is distributed by the American College of Surgeons. Using IOC, we found that 94% of the complications were related to IOC. In the non-IOC group, 94% of the complications were related to the procedure. This would suggest that IOC complications are potentially associated with IOC use. However, many complications were related to the procedure and not IOC use, as many complications were related to the procedure and not to IOC use.

Figure 5. Cost per common bile duct injury (CBDI) avoided at the full range of reported rates of injuries avoided. IOC, intraoperative cholangiography.
costly; values to the right of zero indicate that IOC is more costly. With the exception of the cost of repair (which was varied by more than $250,000), parameters in the model related to events after CBD injury had little impact on the difference in costs between the two strategies. The most important parameters in the model, attributable risk reduction in injury from IOC use and cost of IOC, were varied over a range of estimates and graphed to show their effect on the cost per CBD injury avoided. Figure 5 shows the expected increased cost of LC over a range of values for the cost of IOC. Over the range of costs found in the literature ($77 to $738), the cost per CBD injury avoided ranges from $57,846 to $554,417. This demonstrates that variability in the cost estimates of IOC greatly influence whether or not it is cost effective to perform IOC. To help characterize the settings in which it might be of benefit to incur the increased cost per injury avoided associated with IOC use, these figures should be considered in the context of the cost of an injury. At a cost of injury greater than the cost per injury avoided, performing routine IOC use would provide cost savings.

**DISCUSSION**

Although routine cholangiography will not eliminate all CBD injuries, as demonstrated by two recent population-based analyses, use of cholangiography during LC is associated with a lower rate of CBD injury. Routine IOC use is currently not the standard of care in the United States and these preliminary, observational studies should not be used to determine cause and effect. Despite this, in certain instances (eg, for surgeons who have performed a small number of LCs and for cases complicated by comorbidity), it appears the decrease in injury rate is even more notable. A randomized prospective analysis of cholangiography during LC would be helpful in addressing its true costs and benefits, but such an analysis is impractical because of the infrequency of CBD injury. For example, to demonstrate a 50% reduction in the rate of CBD injury with a power of 90% would require a trial of more than 26,000 patients. When obtaining prospective data is not feasible, modeling techniques are particularly helpful. This modeled analysis attempts to clarify the magnitude of the cost of IOC and when that increased cost might be warranted. Using this form of cost analysis, the cost per CBD injury avoided with IOC use is $87,143 (about $61,000 for less experienced surgeons). When considered in the context over other interventions, this study suggests that routine IOC should be considered a cost favorable intervention.

Determining the cost of an intervention requires an appraisal of the costs of both the IOC and CBD injury itself. Unfortunately, there is wide variability in the reported cost of IOC and in the ways the costs of CBD injury are assessed. As a result, casual “back of the envelope” determinations of cost effectiveness are difficult to critique. For example, several authors have speculated that any cost of IOC would be worthwhile because in addition to the direct costs of CBD injury, the costs of litigation are very high. Injury to the CBD is the sixth most expensive malpractice claim to litigate, with median jury awards of $500,000 and out-of-court settlements of $250,000. These costs are important to acknowledge, but they are not included in this analysis because these are generally factored into health care costs. If this broader societal perspective was considered, other costs associated with injury might also be considered, such as loss of work, caretaker costs, loss of eventual productivity, pain and suffering, and court claims. Rossi and coworkers studied the social outcomes of 11 patients with CBD injury after LC. The range of lost workdays was 90 to 217, with 3.4 admissions, and average hospitalizations of 28.6 days. Two of 11 patients in this series lost their jobs because of absence from work. Anecdotal evidence suggests a marked number of disability claims after CBD injury. A range of compensation awards ($125,000 to $800,000) was noted in representative cases from five different states. Although such societal perspective approaches are important, the data are too inconsistent to evaluate and were not included in this analysis. The model used in this study examined the payer perspective of costs and found a cost per injury avoided that seems to suggest routine IOC use might be warranted despite its increased cost.

Determining whether the cost of an intervention favors its use requires an appreciation of the costs of other therapeutic interventions. Most often, cost analyses compare the cost per a year of life saved (adjusted for the measured quality of life or utility) of the intervention to other known interventions. Death is an infrequent occurrence after CBD injury, but because most people undergoing cholecystectomy are young, the cost per quality-adjusted life year saved is relatively low: $13,500 (assuming that patients return to perfect health after recovering from CBD repair). In general, interventions that provide patients with one quality-adjusted life year
for less than $50,000 (dialysis, seat-belts, etc) are generally considered cost effective.\textsuperscript{20,21}

In light of the high costs of litigation, medical care, and lost productivity, another way to frame the costs of IOC might be considered. Because of the high legal profile of such cases, for surgeons, patients, and payers, the cost per CBD injury avoided can be a more meaningful measure. Unfortunately, this is a framework for evaluation that makes it difficult to compare IOC with other interventions. Based on the legal implication of CBD injury in situations in which LC can be performed with a cost increase of less than $100,000 per injury avoided, many might consider it to be cost "favored." This criterion is met when more than 12 injuries are avoided per 10,000 LCs (at an IOC cost of $122) or IOC costs less than $135 (with an absolute risk reduction of CBD injury with IOC of 0.14%).

The model chosen has several sources of bias. The use of IOC can also influence the severity\textsuperscript{2} of injury (and the frequency of CBD injury), and less severe injuries might "cost" less. But because it is difficult to estimate costs of different types of injuries, we incorporated all repairs into a common cost. This likely overestimates the repair costs associated with injuries occurring when an IOC was used. In addition, some have suggested that increased use of IOC might increase costs by finding a higher rate of positive findings.\textsuperscript{3} These cholangiographic defects might suggest CBD stones but might be clinically irrelevant. Most cholangiographic findings can be cleared with a gentle saline flushing of the biliary system and would increase cost and operating time by only a small amount.\textsuperscript{4} It is also unclear what the fate of these CBD stones would be if left undetected. They can indeed pass into the small bowel without clinical sequelae, or require further endoscopic management with a separate set of associated costs. The results of this analysis provide an estimate of the costs associated with a prevented CBD injury over a range of possible costs of IOC. Estimates of IOC cost from the literature, Washington State claims data, and this analysis support a cost of IOC of less than $125. To determine whether IOC is cost effective at a particular institution, local costs of IOC can be compared with the base-case and calculated from the sensitivity model for IOC cost (Fig. 5). Many of the rates of adverse outcomes come from series that were published in the early 1990s and might reflect an earlier experience with CBD injury. To control for this, we included a broad range of probabilities in the sensitivity analysis to account for the full spectrum of outcomes and costs that might be applicable to this issue.

The cost implications of routine IOC use are difficult to determine. A recently published,\textsuperscript{22} more simplified analysis balancing the costs of IOC and the costs of CBD injury suggested that routine IOC use seemed cost effective. In that study, Podnos and colleagues\textsuperscript{22} estimated the rate and cost of CBD injury based on referral patterns to a single tertiary facility in Orange County. They found that the costs of injury repair outweighed the theoretic costs of IOC use and extrapolated from that finding that the savings from routine IOC use in the United States would be between $38 and $784 million. Although we agree with the conclusion that routine IOC use should be considered cost effective, our study accounts for the types of variability in cost and point probability that are important in performing adequate cost analysis. Accurate assessments of cost effectiveness are dependent on highly variable cost data and probability estimates. The analytic framework provided in this model provides a means to recognize and define patient populations and practice settings where the cost of IOC and the reduction in CBD injury rates make IOC cost-effective.

Lower rates of CBD injury are associated with the use of IOC,\textsuperscript{4,5} yet it remains to be determined if the broader use of IOC will actually prevent CBD injuries. If the association of IOC and CBD protection proves to be causal, then the question of IOC's cost effectiveness becomes important. Using best estimates from the literature and population-based data, IOC use appears to be cost effective when considered in the context of the costs associated with injury. Individual surgeons and institutions can use this information to determine if IOC use is cost effective in their unique practice environments.

Author Contributions
Study conception and design: Flum, Veenstra, Flowers
Acquisition of data: Flum, Veenstra, Flowers
Analysis and interpretation of data: Flum, Veenstra, Flowers
Drafting of manuscript: Flum, Veenstra, Flowers
Critical revision: Flum, Veenstra, Flowers
Statistical expertise: Flum, Veenstra, Flowers

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