OPEN

Economic Evaluation of Pharmacologic Pre- and Postconditioning With Sevoflurane Compared With Total Intravenous Anesthesia in Liver Surgery: A Cost Analysis

Klaus Eichler, MD, MPH,* Martin Urner, MD,† Claudia Twerenbold, MD,*† Sabine Kern,*
Urs Brügger, PhD,† Donat R. Spahn, MD,† Beatrice Beck-Schimmer, MD,† and Michael T. Ganter, MD‡

BACKGROUND: Pharmacologic pre- and postconditioning with sevoflurane compared with total IV anesthesia in patients undergoing liver surgery reduced complication rates as shown in 2 recent randomized controlled trials. However, the potential health economic consequences of these different anesthesia regimens have not yet been assessed.

METHODS: An expostcost analysis of these 2 trials in 129 patients treated between 2006 and 2010 was performed. We analyzed direct medical costs for in-hospital stay and compared pharmacologic pre- and postconditioning with sevoflurane (intervention) with total IV anesthesia (control) from the perspective of a Swiss university hospital. Year 2015 costs, converted to US dollars, were derived from hospital cost accounting data and compared with a multivariable regression analysis adjusting for relevant covariables. Costs with negative prefix indicate savings and costs with positive prefix represent higher spending in our analysis.

RESULTS: Treatment-related costs per patient showed a nonsignificant change by −12,697 US dollars (95% confidence interval [CI], 10,956 to −36,352; $P = .29$) with preconditioning and by −6139 US dollars (95% CI, 6723 to −19,000; $P = .35$) with postconditioning compared with the control group. Results were robust in our sensitivity analysis. For both procedures (control and intervention) together, major complications led to a significant increase in costs by 86,018 US dollars (95% CI, 13,839-158,198; $P = .02$) per patient compared with patients with no major complications.

CONCLUSIONS: In this cost analysis, reduced in-hospital costs by pharmacologic conditioning with sevoflurane in patients undergoing liver surgery are suggested. This possible difference in costs compared with total IV anesthesia is the result of reduced complication rates with pharmacologic conditioning, because major complications have significant cost implications. (Anesth Analg 2017;XXX:00–00)

Today's novel therapeutic approaches should be evaluated for clinical, but also for their economic outcome, because value of health care becomes an important decision criterion in many health care settings.[1] Postoperative complications and associated prolonged length of hospital stay are predominant drivers of total in-hospital costs.[2,3] Strategies reducing postoperative complications are therefore of major interest for the patient's benefit as well as for economic reasons. Such strategies also include perioperative anesthesia management.

The availability of a short-acting, well-controllable IV anesthetic agent such as propofol might influence the anesthesiologists to favor total IV anesthesia over inhalational agents. This preference is further supported by concerns about postoperative nausea and vomiting,[4] about potentially harmful effects by occupational exposure[5,6] (resulting in the need of gas-scavenging systems), and about potential environmental pollution caused by volatile anesthetics.[7]

Volatile anesthetics, however, have been shown to be beneficial in scenarios of ischemia–reperfusion injury.[8,9] Data of a longitudinal study of 34,310 coronary artery bypass graft interventions show that inhalation anesthesia improves survival.[10] Similar results have been found in patients undergoing lung surgery: the administration of volatile anesthetics during 1-lung ventilation immunomodulated hypoxia/reoxygenation-induced tissue damage and resulted in a better postoperative outcome defined by fewer postoperative complications.[11,12] However, there are also studies in which volatile anesthetics failed to exert beneficial effects.[13–15] As a result of this, and the fact that the underlying molecular mechanisms of the protective effects are currently only partially understood, the clinical relevance of pre-/postconditioning with volatile anesthetics remains still controversial.

From the *Winterthur Institute of Health Economics, Zurich University of Applied Sciences, Winterthur, Switzerland; †Institute of Anesthesiology, University of Zurich, Zurich, Switzerland; and ‡Institute of Anesthesiology and Pain Medicine, Kantonsspital Winterthur, Winterthur, Switzerland.

Accepted for publication November 10, 2016.

Funding: This study is supported by Swiss National Science Foundation grant 32003B_135591.

Conflicts of Interest: See Disclosures at the end of the article.

Klaus Eichler, MD, MPH, and Martin Urner, MD, are cofirst authors.

Reprints will not be available from the authors.

Address correspondence to Klaus Eichler, MD, MPH, Winterthur Institute of Health Economics, Zurich University of Applied Sciences, Gertrudstrasse 15, P.O. Box, CH 8401 Winterthur, Switzerland. Address e-mail to eich@zhaw.ch.

DOI: 10.1213/ANE.0000000000001814

In 2 recent randomized controlled trials (RCTs), pharmacologic pre- and also postconditioning with volatile anesthetics has now been featured as promising hepatoprotective strategies in elective liver surgery.[16,17] In these studies, preconditioning with sevoflurane substantially reduced the overall complication rate as well as the rate of major complications in patients undergoing liver resection. For the postconditioning approach, results were similar.[17]

The economic effect of complications of major gastrointestinal surgical procedures such as pancreas or liver surgery on hospital treatment costs is well described.[3] However, we are not aware of studies that assessed the health economic effects of pre- or postconditioning with volatile anesthetics to avoid such complications. We hypothesized that interrupting propofol anesthesia and adding a short pharmacologic pre- or postconditioning with the volatile anesthetic sevoflurane leads to reduced treatment costs in patients undergoing liver surgery in a tertiary center compared with total IV anesthesia without pharmacologic conditioning. Thus, we performed an expostcost analysis of these 2 published RCTs.[16,17]

METHODS

We used data of 2 published RCTs that were approved by the institutional review board for human studies and internationally registered at Clinical Trials.gov NCT00516711[16] and NCT00518908.[17] Written informed consent had been obtained from all subjects. According to the regional ethical board, no additional ethical approval was needed for this ex post health economic analysis.

Design and Comparison of Alternatives

A cost analysis was performed focusing on direct medical costs for in-hospital stay for patients without liver cirrhosis undergoing elective liver resection with inflow occlusion. We compared (1) direct medical costs of pharmacologic pre- and postconditioning with sevoflurane with (2) direct medical costs of total IV anesthesia, the control group in the published RCTs.

Setting

The 2 RCTs were conducted at the University Hospital Zurich, Zurich, Switzerland. Patients were followed during their in-hospital stay. No outpatient data were assessed. Consecutive patients without liver cirrhosis undergoing elective liver resection with inflow occlusion between April 2006 and November 2007[16] and between January 2008 and September 2010[17] were included. All patients undergoing laparoscopic liver resection and/or emergency surgery (safety concerns) were excluded.

Surgical Intervention

In both RCTs, liver resection was performed with the use of the Pringle maneuver. This technique implies clamping the hepatic artery and the portal vein to diminish blood loss during resection. However, at the same time, the maneuver triggers hepatic apoptosis and necrosis known as ischemia–reperfusion injury.[18,19] The surgical procedures were performed in a standardized manner under the supervision of 2 experienced hepatopancreatobiliary surgeons and are described elsewhere in detail.[16,17] Briefly, in the preconditioning setting, the time point of 30 minutes before clamping of the portal triad was defined by the surgeon while mobilizing the liver and communicated to the anesthesiologist. In both clinical trials, inflow occlusion was performed using the tourniquet method with a 4-mm Mersilene tape applied around the portal triad. The time of continuous inflow occlusion lasted for at least 30 minutes and was adapted if necessary on request of the surgeon. During resections, central venous pressure was adjusted to low levels between 0 and 5 mm Hg. All individuals (surgeons, nurses, and physicians on the ICU) were blinded for group allocation to exclude potential bias. Patients were admitted to the ICU according to clear criteria defined by institutional standards.

Anesthesia Procedures

Both RCTs had assessed the effect of sevoflurane pre- or postconditioning compared with total IV anesthesia. Details of the general anesthesia procedures are described in the RCT publications.[16,17] Briefly, in the control groups, anesthetic induction and maintenance were conducted using target-controlled infusion of propofol and bolus application of fentanyl, remifentanil, and atracurium following a well-defined protocol according to the clinical needs.

In the intervention groups of both clinical trials, propofol anesthesia was replaced by sevoflurane for an overall time interval of 30 minutes. In patients with preconditioning, the administration of sevoflurane was applied in the 30 minutes before hepatic inflow occlusion. In the postconditioning group, patients were exposed to sevoflurane immediately on reperfusion of the liver (end of the Pringle maneuver). In both trials, propofol infusion was reinitiated when sevoflurane application was stopped. In both trials, end-expiratory sevoflurane concentrations of 3.2 vol % were targeted during 10 minutes (according to a minimal alveolar concentration of 1.5).

The primary clinical outcome of the 2 RCTs was postoperative alanine aminotransferase or aspartate aminotransferase peak, which were both significantly reduced with pharmacologic pre- or postconditioning. Even more important, a relevant clinical benefit of similar magnitude emerged in both studies. Fewer complications occurred in the intervention group compared with the control group. This was the case for any complications (eg, preconditioning: odds ratio, 0.46 [95% confidence interval, {CI}, 0.25–0.85]; $P = .006$)[16] and for major complications (eg, postconditioning: odds ratio, 0.22 [95% CI, 0.05–0.97]; $P = .045$).[17]

Subjects and Data Collection

Patients undergoing elective liver resection with inflow occlusion were included in the cost analysis. Data of the 2 RCTs were pooled, because pharmacologic pre- and postconditioning implies the same protective principle. For the 3-arm postconditioning trial,[17] we excluded the third randomized group (intermittent clamping group: equivalence part of that study) for our cost analysis to isolate the pharmacologic effect of sevoflurane conditioning.

Data for age, gender, American Society of Anesthesiologists physical classification as well as Charlson index, reflecting patients' comorbidities,[20] were available. Important data from the surgical procedure were used such as time of surgery, time of Pringle maneuver, and intraoperative blood loss. Furthermore, length of ICU and hospital stay were measured.

For our cost analysis, major complications were defined according to the Clavien-Dindo classification (Appendix Table A1) as Grade IIIb complications requiring an intervention under general anesthesia, Grade IV complications with single- or multiorgan failure, or Grade V defined as death.[21] This outcome is well established via the treatment-oriented complication score (www.surgicalcomplication.info).

Health Economic Assessments

Direct health care costs (ie, in-hospital treatment costs, including ICU, covering costs for staff and materials) were the economic outcome. Indirect costs resulting from loss of productivity of patients were not included.

For cost calculations, we applied prospectively collected time units (eg, time for nursing and anesthesia services), units of other resources (eg, drugs or medical materials), and prices via the hospital cost accounting system during the study periods (2006–2007 and 2008–2010) that had not yet been analyzed for health economic questions. Costs were calculated according to Swiss standard procedures for hospital cost accounting.[22,23] For example, labor costs for nurses are derived by multiplying prospectively documented nursing time units by current nursing wages; costs for drugs (eg, anesthetics) and medical materials (eg, diagnostic tests, blood products) are derived by counting units of applied resources multiplied by current Swiss unit prices. For the intervention itself, this means that sevoflurane costs were derived from calculations based on estimated average drug volume (6.75 mL for 30 minutes—according to recommendations of the Swiss Society of Anesthesiologists) referring to current Swiss prices.[24] When adding sevoflurane, the cost for propofol was not reduced in our calculation. No additional costs were assigned to the intervention, because no supplementary technical equipment or extra staff time was needed. Sevoflurane costs are part of the cost element "cost medication and materials" and are reported separately.

Some additional cost components (eg, for administration) are allocated as a fixed rate to each patient. Data for interest and capital costs were excluded. We did not rely on hospital billing data, because at that time, billing data reflected the result of negotiations between providers and health insurance companies and not costs of resource consumption. None of the patients was hospitalized before surgery to receive tests or services directly related to the liver surgery under study. Thus, no additional costs were included.

We performed 3 sensitivity analyses: We excluded patients who had died (complication Grade V), because they might show relatively low costs as a result of a sometimes rapid fatal clinical course. In addition, we excluded 2 outliers with extremely high costs and patients with minor complications.

For the health economic evaluation, we chose the perspective of the University Hospital Zurich, because the RCTs were performed with patients from that hospital. The Swiss prices from 2006 to 2010 were inflated to 2015 Swiss prices using the annual rates of the medical component of the Swiss consumer price index.[25] All costs are presented in 2015 US dollars (applying the official 2015 currency conversion rate of 1.04 to convert 2015 Swiss Francs (CHF) into 2015 US dollars).[26] Current standards for performing health economic evaluations were applied.[27,28]

Statistical Analysis

For our descriptive analysis, we used means (standard deviation) or medians (interquartile range [IQR]) for continuous variables and proportions for categorical data. For inferential analysis of cost data, we calculated 95% CI[29] as a measure of uncertainty using the nonparametric bootstrap with 2000 replicates.[30] This resampling method is recommended for analysis of means of skewed cost data.[30] For other data, we applied standard parametric and nonparametric tests, as suitable.

For our cost comparison, we used a stepwise approach: First, cost data were assigned to each patient. Second, we calculated the mean treatment costs for both groups. Third, a multivariable linear regression model was used to assess the association between costs (dependent variable) and treatment (ie, intervention vs control) adjusting for confounding factors. We used 2 data sets of different time periods with a slightly different intervention (pre- and postconditioning). To take this into account and to adjust for unobserved factors that might have differed between trials, we introduced a dummy variable for mode of conditioning and an interaction term with the treatment. The fit of the model was optimized by forming classes over age and Charlson index. Akaike information criterion statistics was used to avoid overadjustment. In the final model, American Society of Anesthesiologists class and Charlson index were kept as confounding factors.

Blinding for group allocation in the preconditioning trial was applied for the hospital cost accounting team as well as for health economic analysts. The code for group allocation had not been broken before the cost analysis was finished. For the postconditioning trial, the hospital cost accounting team was blinded for group allocation, whereas blinding of the health economic analysts was not possible. Data analysis was conducted with the STATA SE 14 software package (StataCorp, 2014; Stata Statistical Software, College Station, TX).

RESULTS

Included Patients and Clinical Course

Overall, 129 patients were analyzed (Figure 1) including data of 64 patients from the preconditioning trial (n = 30 intervention group; n = 34 control group)[16] as well as of 65 patients from the postconditioning trial (n = 48 intervention group; n = 17 control group).[17] Baseline data and intraoperative characteristics of all 129 patients showed that patients randomized to the intervention were somewhat younger, but they had a somewhat higher mean Charlson index (Table 1). Blood loss was reduced in the intervention group, but the difference was not statistically significant.

Significantly fewer complications occurred in the intervention group compared with the control group (any complication: 28% vs 67%; absolute risk reduction [ARR] 39% [95% CI, 22–55]; number needed to treat [NNT] 3 [95% CI, 2–5]; $P < .001$; Table 2). Also the rate of major complications (defined as Class IIIb–V) decreased significantly in the

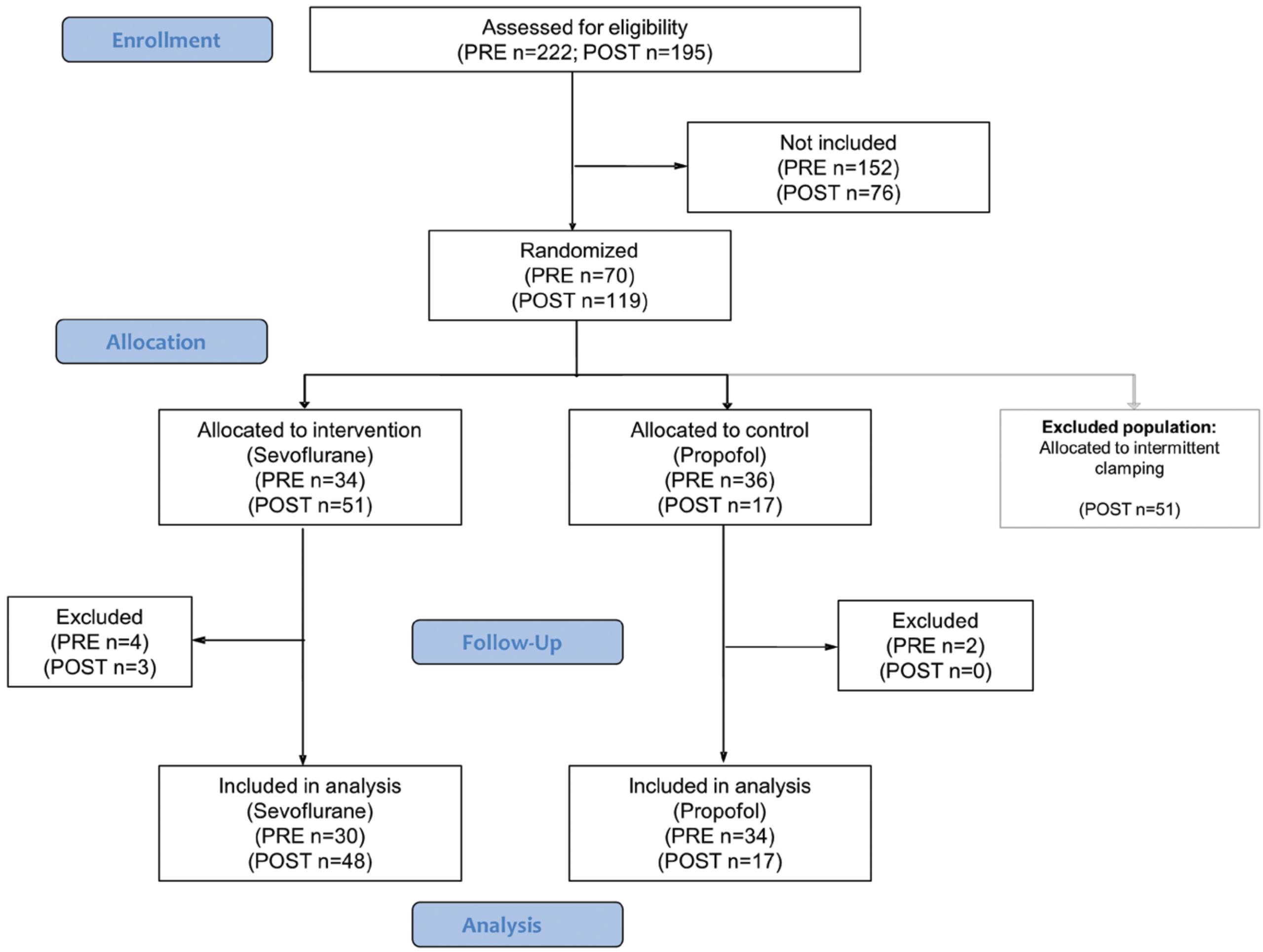

Figure 1. Flow of participants through study. The prospectively collected clinical and cost data of 2 published randomized controlled trials were used.[16,17] For the postconditioning trial population, the intermittent clamping group (equivalence part of that study) was excluded to isolate the pharmacologic effect of sevoflurane conditioning. PRE indicates preconditioning trial; POST, postconditioning trial.

Table 1. Baseline Data and Intraoperative Characteristics of Patients

	Intervention (n = 78)	Control (n = 51)	*P* Value
Gender			
Men, no. (%)	44 (56.4)	31 (60.8)	.62
Age			
Years, mean (SD)	57.5 (13.4)	57.8 (12.8)	.90
ASA			
Mean (SD)	2.20 (0.54)	2.22 (0.54)	.81
Class I/II/III (no.)	5/53/20	3/34/14	.97
Charlson index (0–37)			
Mean (SD)	4.95 (2.7)	4.61 (2.8)	.69
Duration of operation			
Min, mean (SD)	278 (81.6)	283 (99.8)	.76
Duration of Pringle maneuver			
Min, mean (SD)	34 (7.6)	35 (7.0)	.86
Blood loss			
mL (SD)	310 (296)	353 (320)	.30

Abbreviations: ASA, American Society of Anesthesiologists physical classification; Charlson index, reflecting patients' comorbidities (with higher scores indicating higher predicted 10-year mortality); ICU, intensive care unit; SD, standard deviation.

intervention group (major complications: 6% vs 24%; ARR 18% [95% CI, 4–30]; NNT 6 [95% CI, 4–24]; *P* = .005).

Mean total hospital stay (ie, ICU stay plus floor stay) was significantly shorter in the intervention group compared with the control group (11.0 vs 13.6 days; absolute difference: –2.6 days; *P* = .02; Table 2). In the control group, twice as many patients had to be treated postoperatively in an ICU (9 of 51 vs 4 of 78 patients). For the preconditioning group, the shorter hospital stay of the intervention group was mainly because of shorter ICU stay (mean ICU stay: 0.5 vs 1.7 days; −1.2 days; *P* = .16; floor stay: 10.5 vs 11.1; –0.6 days; *P* = .53). Data for length of ICU stay were not available for the postconditioning patients.

Costs

Mean treatment-related costs (Table 3) were lower for patients in the intervention group (unadjusted mean costs $41,439 [median: 28,588; IQR, 20,928–39,340]) compared with the control group (unadjusted mean costs $44,454 [median: 27,812; IQR, 21,560–46,413]). Main cost components were costs for physician and nursing wages, for

Table 2. Complications and Length of Stay

	Intervention (n = 78)	Control (n = 51)	Absolute Risk Reduction[a] (95% CI)	Number Needed to Treat (95% CI)	*P* Value
Complications					
Any, no. (%)	22 (28)	34 (67)	39% (22 to 55)	3 (2 to 5)	<.001
Major (IIIb–V), no. (%)	5 (6)	12 (24)	18% (4 to 30)	6 (4 to 24)	.005
Length of hospital stay			**Absolute Difference[a]**		
Days (mean; SD)	11.0 (8.6)	13.6 (8.6)	−2.6 (8.7)		.02[b]
Length of ICU stay[c]					
Days (mean; SD)	0.5 (2.0)	1.7 (5.4)	−1.2 (4.2)		.16[b]
Length of floor stay[c]					
Days (mean; SD)	10.5 (2.0)	11.1 (5.4)	−0.6 (5.1)		.53[b]

Abbreviations: CI, confidence interval; ICU, intensive care unit; SD, standard deviation.
[a]Intervention versus control.
[b]Wilcoxon rank-sum test (intervention vs control).
[c]Data available for 64 patients with preconditioning (n = 30 intervention; n = 34 control); thus, data may not add up to "length of hospital stay."

Table 3. Costs

Costs (mean [SD], if not indicated otherwise)	Intervention n = 78	Control n = 51
Total treatment-related costs ($)[a] Mean (SD), unadjusted value	**41,439 (69,283)**	**44,454 (54,370)**
Costs physician wages ($)	9207 (22,150)	9952 (15,129)
Costs nursing ($)	9526 (23,015)	10,226 (15,488)
Costs medication and materials ($)	7979 (10,584)	8025 (8517)
Thereof, costs of sevoflurane (intervention; $)	6.38	...
Costs devices ($)	120 (399)	353 (1773)
Costs other nonhospital services ($)	176 (878)	90 (213)
Costs hotellerie ($)	1147 (1088)	1273 (1419)
Costs technical services ($)[b]	9333 (7618)	10,580 (10,766)
Costs administration ($)	3953 (5672)	3954 (4717)
Preconditioning intervention: Cost reduction for treatment-related costs ($) Mean (95% CI); adjusted value,[c] compared with control	**−12,697 (10,956 to −36,352); *P* = .29**	
Postconditioning intervention: Cost reduction for treatment-related costs ($) Mean (95% CI); adjusted value,[c] compared with control	**−6139 (6723 to −19,000); *P* = .35**	

Abbreviations: CI, confidence interval; SD, standard deviation.
[a]Treatment-related costs include all costs during the index hospitalization for liver surgery: physician and nursing wages, surgery, anesthesia, diagnostics, drugs, blood products, devices, other materials, ICU care, ward care, costs for other technical services, and administration. $ = US dollars.
[b]Technical services include operation theater, intensive care unit, emergency ward, radiologic services, laboratory services, diagnostic services, and allied health professionals such as occupational therapists, physiotherapists.
[c]Multivariable linear regression model.

Table 4. Treatment-Related Costs According to Complication Category

	Total Treatment-Related Costs ($)[a] (unadjusted values) Mean (SD) (n = 129)
All patients (n = 129)	42,632 (63,596)
Without complications[b] (n = 73)	28,720 (16,886)
With minor complications[b] (I–IIIa; n = 39)	36,116 (14,973)
With major complications[b] (IIIb–V; n = 17)	117,313 (153,714); *P* = .02[c]

Abbreviation: SD, standard deviation.
[a]Treatment-related costs include all costs during the index hospitalization for liver surgery: physician and nursing wages, surgery, anesthesia, diagnostics, drugs, blood products, devices, other materials, intensive care unit care, ward care, costs for other technical services, and administration. $ = US dollars.
[b]According to the Clavien-Dindo classification.
[c]Compared with "no major complication" (ie, "without complication" or "with minor complications").

medication and materials as well as for technical services in both groups. Estimated costs of the intervention itself were $6.38 per patient.

After adjustment for relevant covariables with a multivariable regression analysis, treatment-related costs in the intervention group showed a nonsignificant change by $−12,697 (95% CI, 10,956 to −36,352; $P = .29$) with preconditioning and by $−6139 (95% CI, 6723 to −19,000; $P = .35$) with postconditioning. No significant cost difference emerged between the pre- and postconditioning interventions ($P = .84$).

Predictors of costs were a higher American Society of Anesthesiologists (ASA) score (reference: ASA I; ASA II: $P = .01$; ASA III: $P = .02$) as well as a high Charlson index (reference: Charlson ≤3; Charlson > 10: $P < .001$). The suggested difference in treatment costs between intervention and control group (with postconditioning: $−6,100; with preconditioning $−12,700) was equivalent to about 13% or 27% of treatment related costs of the control group.

Distribution of costs showed 2 extreme outliers with costs of more than $230,000. One patient in the intervention group (postconditioning) showed costs of $616,153. This patient was in the hospital for 74 days, including ICU care (main complication: IVb; additional complications: IVa, IVa, and IIIa). Similarly, 1 patient in the control group of the preconditioning trial showed costs of $371,325. This patient was in the hospital for 45 days, of which 30 days were with ICU care (main complication: IVb; additional complications: IVa, IIIb, and II).

Increasing severity of complications was related to increasing costs as a general trend (Table 4). Although minor complications contributed little to increased costs compared with patients with no complications, major complications

Table 5. Treatment-Related Costs According to Major Complications

	Intervention		Control	
	Major Complications[a] No	Major Complications[a] Yes	Major Complications[a] No	Major Complications[a] Yes
Preconditioning trial (n = 30 and n = 34; N = 74)	n = 28	n = 2	n = 25	n = 9
Total treatment-related costs ($)[b]	32,054	74,878	25,253	104,021
Postconditioning trial (n = 48 and n = 17; N = 65)	n = 45	n = 3	n = 14	n = 3
Total treatment-related costs ($)[b]	31,813	251,151	38,910	51,643
All patients (n = 78 and n = 51; N = 129)	n = 73	n = 5	n = 39	n = 12
Total treatment-related costs ($)[b]	31,906	180,642	30,155	90,927

[a]Major complications include complication Classes IIIb–V according to the Clavien-Dindo classification; "major complications no" include patients with no complications or with minor complications.
[b]Treatment-related costs include all costs during the index hospitalization for liver surgery: physician and nursing wages, surgery, anesthesia, diagnostics, drugs, blood products, devices, other materials, intensive care unit care, ward care, costs for other technical services, and administration.
$ = US dollars; costs are unadjusted, mean treatment-related costs.

were a substantial cost driver. This also held when pre- and postconditioning data were depicted for intervention and control patients separately (Table 5). Patients without major complications (n = 112) showed average costs of $31,296 (standard deviation 16,559), but costs increased considerably if major complications occurred (mean: $117,314 [standard deviation 153,714]; n = 17). Such a difference of $86,018 (95% CI, 13,839–158,198; *P* = .02) is highly relevant for hospitals.

In our sensitivity analysis, the results of the main analysis showed to be robust (Appendix Table A2). However, the exclusion of 39 patients with minor complications led to increased costs in the postconditioning intervention group of $2501 [95% CI, 22,585 to −17,584]; *P* = .81) compared with the control group as a result of the increased weight of 1 patient in the postconditioning intervention group with major complications and extremely high costs of $616,153.

DISCUSSION

The present cost analysis suggests that pre- and postconditioning with sevoflurane can result in relevant cost savings when compared with total IV anesthesia in patients undergoing elective liver resection with inflow occlusion. Major complications had a significant effect on costs.

Strengths and Limitations of Our Approach

Our study shows several methodological strengths: (1) All consecutive patients of a single tertiary center who met the inclusion criteria were included in the trial. This contributes to the external validity of results for other centers with specialized hepatic surgery. (2) Both trials show a clinical effect of similar magnitude. (3) Our statistical model takes into account the fact that data are derived from 2 trials performed at different time points (2006–2007 and 2008–2010) and adjusts for unobserved differences in postoperative care and cost accounting over time. This makes our findings more robust.

Several methodological limitations have to be mentioned: First, applied data are from the period 2006 to 2010. However, we adjusted cost data for inflation until 2015 using the medical component of the Swiss consumer price index. Second, the available sample size is underpowered for a health economic analysis, because the sample sizes of the 2 RCTs were calculated for a biochemical marker as the primary endpoint (alanine aminotransferase, aspartate aminotransferase) and not for a cost outcome. At a bigger sample size, it is more likely that the demonstrated difference in total treatment-related costs becomes statistically significant as well. Finally, despite a suitable randomization procedure in both trials, an imbalance in some of the confounding patient parameters emerged between groups, presumably because of the small sample size. However, we applied a suitable statistical adjustment for relevant confounders in our model to overcome possible bias.

Protective Effects of Volatile Anesthetics

The clinical relevance of the protective effects provided by volatile anesthetics is the subject of an ongoing debate that has lasted for 3 decades.[31] In cardiac surgery, the use of volatile anesthetics is associated with a reduced risk of all-cause mortality and of myocardial infarction.[32] Beside the beneficial effects in liver surgery, there is also sound evidence on neuroprotection and protection exerted by volatile anesthetics against ischemic acute kidney injury.[33,34] However, in a large study comparing volatile anesthetics versus total IV anesthesia, no overall benefit for patients undergoing noncardiac surgery could be demonstrated.[35] In addition, there is also solid concern about increased apoptosis and formation of β-amyloid protein in neuronal tissue induced by volatile anesthetics.[36] The reason for this contradictory evidence base is that the underlying molecular mechanisms are currently not understood fully.[37] Several mechanisms have been proposed, which might be responsible for the beneficial effects such as a different regulation of energy metabolism mediated by mitochondrial potassium channels[38] and/or a modulation of effector cell adhesion[39] and function[40,41] induced by volatile anesthetics. There is also some evidence that not the ether basic structure, but parts of the halogenation of volatile anesthetics and of their metabolites might be responsible for altered host response to tissue injury.[42]

In this study, we investigated the effects of sevoflurane pre- and postconditioning and might therefore not be able to generalize the results for all volatile anesthetics. Also, in both RCTs, the patients were exposed to sevoflurane during a time period of only 30 minutes. In other studies, however, volatile anesthetics were used for the entire duration of the anesthesia and no protective effects compared with propofol anesthesia were observed. This suggests that the duration of exposure to volatile anesthetics might be a crucial factor with regard to the exertion of potential protective effects (on/off vs exposure during entire procedure).[43–45] In addition, only the beneficial effects, most probably, become apparent in patients who have been exposed to a relevant ischemia–reperfusion or hypoxia/reoxygenation injury.

The ARR of major complications was 18% (95% CI, 4–30) resulting in a NNT of 6 patients. Major complications, however, are a significant cost driver, as shown in our study and also for liver surgery in a previous publication.[3] Thus, besides the avoidance of detrimental effects for patients, prevention of complications is of high economic importance. In contrast, direct costs of anesthesia with volatile anesthetics range at very low prices between $12 and $23 per hour.[46,47] We are not aware of another health economic evaluation, which has assessed the economic effects of pharmacologic conditioning with volatile agents in major surgical interventions. Graham et al[48] have performed health economic evaluations assessing the economic effect of N_2O-free anesthetics. Their cost–benefit analysis showed lower treatment costs resulting from lower complication rates, although the costs of N_2O-free anesthetics were higher when compared with the conventional procedures with N_2O.[48] More health economic evaluations have to be performed to better understand the relationship between the magnitude of patient benefit and costs for innovative approaches in anesthesia. Patient blood management, for example, could be such an approach to be evaluated with sound health economic analyses.[49]

Significance of Findings for Patients and Implications for Decision-Makers

Our results can primarily inform health care decision-makers within the implementing hospital as well as local authorities about the costs of service provision not only in Switzerland, but internationally. Nevertheless, it is worth noting that our results of the in-hospital cost accounting is specific to a Swiss (European) system, where the patient is more likely to stay for a longer portion of recovery as compared with the United States, which emphasizes more rapid discharge to an intermediate level of care such as a rehabilitation hospital or an according nursing facility. In addition, variation in the cost pattern between hospitals may exist because of variable organizational processes, even within a single country. Although in our data set, the difference in costs between intervention and control groups was not statistically significant, such cost savings are economically relevant, because they add up to a substantial sum after repeated treatments. Using a clinical example, clinicians (as health economists and decision-makers) are interested in clinically (financially) relevant differences rather than in statistically significant differences that are not relevant for patients (payers).

No need for further education of the staff or acquisition of new equipment is necessary for pharmacologic conditioning. This is an additional advantage. Thus, for clinicians and the hospital management, promotion of pharmacologic pre- or postconditioning in liver surgery is an attractive option to contemporaneously optimize patient care and resource utilization. Particularly the postconditioning approach represents a feasible method, which does not require detailed planning like in preconditioning, in which the window of sevoflurane application has to be coordinated with the surgical partner. Also in emergency situations, postconditioning can be performed, whereas preconditioning might not be an option.

CONCLUSIONS

In this cost analysis, reduced in-hospital costs by pharmacologic conditioning with sevoflurane in patients undergoing liver surgery are suggested. This possible cost difference is the result of reduced complication rates, because major complications have significant cost implications. These findings can feed the discussion with authorities to allow clinicians to design best practice plans for the treatment of patients. Such information is becoming more important to increase value in health care.[1]

APPENDIX

Table A1. Complication Grades According to the Clavien-Dindo Classification[21]

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions
Grade II	Requiring pharmacologic treatment with drugs other than such allowed for Grade I complications; blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including central nervous system complications[a]) requiring IC/ICU management
Grade IVa	Single-organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of patient

Abbreviations: IC, intermediate care; ICU, intensive care unit; TIA, transient ischemic attacks.

[a]Brain hemorrhage, ischemic stroke, subarachnoidal bleeding, but excluding TIA.

Table A2. Sensitivity Analysis

	Cost reduction for treatment-related costs ($)[a] Mean (95% CI); adjusted value[b]
Complete study population (n = 129)	
Preconditioning intervention (n = 78)	−12,697 (10,956 to −36,352); *P* = .29
Postconditioning intervention (n = 51)	−6139 (6273 to −19,000); *P* = .35
Exclusion of 2 extreme outlier patients with treatment-related costs of >$200,000 (n = 127)	
Preconditioning intervention (n = 77)	−2771 (9748 to −15,292); *P* = .66
Postconditioning intervention (n = 50)	−5599 (6272 to −17,471); *P* = .35
Exclusion of 2 dead patients (n = 127)	
Preconditioning intervention (n = 77)	−14,512 (8414 to −37,437); *P* = .21
Postconditioning intervention (n = 50)	−6550 (6134 to −19,232); *P* = .31
Exclusion of 39 patients with minor complications (n = 90)	
Preconditioning intervention (n = 61)	−23,766 (13,715 to −61,248); *P* = .21
Postconditioning intervention (n = 29)	+2501 (22,585 to −17,584); *P* = .81

Abbreviation: CI, confidence interval.

[a]Treatment-related costs include all costs during the index hospitalization for liver surgery: physician and nursing wages, surgery, anesthesia, diagnostics, drugs, blood products, devices, other materials, intensive care unit care, ward care, costs for other technical services, and administration. $ = US dollars.

[b]Multivariable linear regression model, intervention compared with control.

DISCLOSURES

Name: Klaus Eichler, MD, MPH.
Contribution: This author helped design and conduct the study, collect, analyze and interpret the data, and prepare the manuscript.
Conflict of Interest: None.
Name: Martin Urner, MD.
Contribution: This author helped design and conduct the study, collect, analyze and interpret the data, and prepare the manuscript.
Conflict of Interest: None.
Name: Claudia Twerenbold, MD.
Contribution: This author helped analyze and interpret the data, and revise the manuscript.
Conflict of Interest: None.
Name: Sabine Kern.
Contribution: This author helped conduct the study, collect and interpret the data, and revise the manuscript.
Conflict of Interest: None.
Name: Urs Brügger, PhD.
Contribution: This author helped design the study, analyze and interpret the data, and revise the manuscript.
Conflict of Interest: None.
Name: Donat R. Spahn, MD.
Contribution: This author helped design and conduct the study, collect, analyze and interpret the data, and revise the manuscript.
Conflict of Interest: Dr. Spahn's academic department is receiving grant support from the Swiss National Science Foundation, Berne, Switzerland, the Ministry of Health (Gesundheitsdirektion) of the Canton of Zurich, Switzerland for Highly Specialized Medicine, the Swiss Society of Anesthesiology and Reanimation (SGAR), Berne, Switzerland, the Swiss Foundation for Anesthesia Research, Zurich, Switzerland, Bundesprogramm Chancengleichheit, Berne, Switzerland, CSL Behring, Berne and Switzerland, Vifor SA, Villars-sur-Glâne, Switzerland. Dr. Spahn was the chairman of the ABC Faculty and is the co-chairman of the ABC-Trauma Faculty, which both are managed by Physicians World Europe GmbH, Mannheim, Germany and sponsored by unrestricted educational grants from Novo Nordisk Health Care AG, Zurich, Switzerland, CSL Behring GmbH, Marburg, Germany and LFB Biomédicaments, Courtaboeuf Cedex, France.
Name: Beatrice Beck-Schimmer, MD.
Contribution: This author helped design and conduct the study, collect, analyze and interpret the data, and revise the manuscript.
Conflict of Interest: None.
Name: Michael T. Ganter, MD.
Contribution: This author helped design and conduct the study, collect, analyze and interpret the data, and revise the manuscript.
Conflict of Interest: None.
This manuscript was handled by: Kate Leslie, MD.
Acting EIC on final acceptance: Thomas R. Vetter, MD, MPH.

REFERENCES

1. Porter ME. What is value in health care? *N Engl J Med*. 2010;363:2477–2481.
2. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ; Participants in the VA National Surgical Quality Improvement Program. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg*. 2005;242:326–341.
3. Vonlanthen R, Slankamenac K, Breitenstein S, et al. The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patients. *Ann Surg*. 2011;254:907–913.
4. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N. A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology*. 1999;91:693–700.
5. McGregor DG. Occupational exposure to trace concentrations of waste anesthetic gases. *Mayo Clin Proc*. 2000;75:273–277.
6. Byhahn C, Wilke HJ, Westpphal K. Occupational exposure to volatile anaesthetics: epidemiology and approaches to reducing the problem. *CNS Drugs*. 2001;15:197–215.
7. Ishizawa Y. Special article: general anesthetic gases and the global environment. *Anesth Analg*. 2011;112:213–217.
8. De Hert SG, Turani F, Mathur S, Stowe DF. Cardioprotection with volatile anesthetics: mechanisms and clinical implications. *Anesth Analg*. 2005;100:1584–1593.
9. Landoni G, Greco T, Biondi-Zoccai G, et al. Anaesthetic drugs and survival: a Bayesian network meta-analysis of randomized trials in cardiac surgery. *Br J Anaesth*. 2013;111:886–896.
10. Bignami E, Biondi-Zoccai G, Landoni G, et al. Volatile anesthetics reduce mortality in cardiac surgery. *J Cardiothorac Vasc Anesth*. 2009;23:594–599.
11. De Conno E, Steurer MP, Wittlinger M, et al. Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. *Anesthesiology*. 2009;110:1316–1326.
12. Schilling T, Kozian A, Kretzschmar M, et al. Effects of propofol and desflurane anaesthesia on the alveolar inflammatory response to one-lung ventilation. *Br J Anaesth*. 2007;99:368–375.
13. Fellahi JL, Gue X, Philippe E, Riou B, Gerard JL. Isoflurane may not influence postoperative cardiac troponin I release and clinical outcome in adult cardiac surgery. *Eur J Anaesthesiol*. 2004;21:688–693.
14. Landoni G, Zangrillo A, Fochi O, et al. Cardiac protection with volatile anesthetics in stenting procedures. *J Cardiothorac Vasc Anesth*. 2008;22:543–547.
15. Jakobsen CJ, Berg H, Hindsholm KB, Faddy N, Sloth E. The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. *J Cardiothorac Vasc Anesth*. 2007;21:664–671.
16. Beck-Schimmer B, Breitenstein S, Urech S, et al. A randomized controlled trial on pharmacological preconditioning in liver surgery using a volatile anesthetic. *Ann Surg*. 2008;248:909–918.
17. Beck-Schimmer B, Breitenstein S, Bonvini JM, et al. Protection of pharmacological postconditioning in liver surgery: results of a prospective randomized controlled trial. *Ann Surg*. 2012;256:837–844.
18. Zhai Y, Busuttil RW, Kupiec-Weglinski JW. Liver ischemia and reperfusion injury: new insights into mechanisms of innate-adaptive immune-mediated tissue inflammation. *Am J Transplant*. 2011;11:1563–1569.
19. Datta G, Fuller BJ, Davidson BR. Molecular mechanisms of liver ischemia reperfusion injury: insights from transgenic knockout models. *World J Gastroenterol*. 2013;19:1683–1698.
20. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
21. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
22. Gesundheitsdirektion des Kantons Zürich. *Handbuch Prisma. Wegleitung zur Erhebung des Patientenrecord in der Somatik*. Zürich: Gesundheitsdirektion des Kantons Zürich, 2012; 46–47.
23. H+ Die Spitäler der Schweiz. *Handbuch REKOLE®—Betriebliches Rechnungswesen im Spital*, 4th ed. Bern: H+ Die Spitäler der Schweiz, 2013.
24. SGAR/SSAR. Recommendations for cost analysis of inhalation anesthetics in TARMED. 2008 http://www.sgar-ssar.ch/fileadmin/user_upload/Dokumente/Tarife-DRG/Inhalationsanaesthetikaverbrauch.pdf. Accessed October 1, 2016.
25. Bundesamt für Statistik. Landesindex der Konsumentenpreise. Available at: http://www.LIK.bfs.admin.ch. Accessed September 30, 2016.
26. World Bank. Official exchange rate (LCU per US$, period average). http://data.worldbank.org/indicator/PA.NUS.FCRF. Accessed September 30, 2016.
27. Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd ed. Oxford, UK: Oxford University Press; 2005.
28. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ*. 1996;313:275–283.
29. Altman D, Machin D, Bryant T, Gardner M. *Statistics with Confidence*. *Bristol, UK: BMJ Books*; 2001.
30. Barber JA, Thompson SG. Analysis of cost data in randomized trials: an application of the non-parametric bootstrap. *Stat Med*. 2000;19:3219–3236.
31. Kersten JR. A recipe for perioperative cardioprotection: what matters most? The ingredients or the chef? *Circulation*. 2012;126:2671–2673.

32. Landoni G, Biondi-Zoccai GG, Zangrillo A, et al. Desflurane and sevoflurane in cardiac surgery: a meta-analysis of randomized clinical trials. *J Cardiothorac Vasc Anesth*. 2007;21:502–511.
33. Fukazawa K, Lee HT. Volatile anesthetics and AKI: risks, mechanisms, and a potential therapeutic window. *J Am Soc Nephrol*. 2014;25:884–892.
34. Koerner IP, Brambrink AM. Brain protection by anesthetic agents. *Curr Opin Anaesthesiol*. 2006;19:481–486.
35. Lurati Buse GA, Schumacher P, Seeberger E, et al. Randomized comparison of sevoflurane versus propofol to reduce perioperative myocardial ischemia in patients undergoing noncardiac surgery. *Circulation*. 2012;126:2696–2704.
36. Matchett GA, Allard MW, Martin RD, Zhang JH. Neuroprotective effect of volatile anesthetic agents: molecular mechanisms. *Neurol Res*. 2009;31:128–134.
37. Wu L, Zhao H, Wang T, Pac-Soo C, Ma D. Cellular signaling pathways and molecular mechanisms involving inhalational anesthetics-induced organoprotection. *J Anesth*. 2014;28:740–758.
38. Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Schaub MC. Volatile anesthetics mimic cardiac preconditioning by priming the activation of mitochondrial K(ATP) channels via multiple signaling pathways. *Anesthesiology*. 2002;97:4–14.
39. Lucchinetti E, Ambrosio S, Aguirre J, et al. Sevoflurane inhalation at sedative concentrations provides endothelial protection against ischemia-reperfusion injury in humans. *Anesthesiology*. 2007;106:262–268.
40. Nakagawara M, Takeshige K, Takamatsu J, Takahashi S, Yoshitake J, Minakami S. Inhibition of superoxide production and Ca2+ mobilization in human neutrophils by halothane, enflurane, and isoflurane. *Anesthesiology*. 1986;64:4–12.
41. Welch WD. Halothane reversibly inhibits human neutrophil bacterial killing. *Anesthesiology*. 1981;55:650–654.
42. Urner M, Limbach LK, Herrmann IK, et al. Fluorinated groups mediate the immunomodulatory effects of volatile anesthetics in acute cell injury. *Am J Respir Cell Mol Biol*. 2011;45:617–624.
43. Ko JS, Gwak MS, Choi SJ, et al. The effects of desflurane and propofol-remifentanil on postoperative hepatic and renal functions after right hepatectomy in liver donors. *Liver Transpl*. 2008;14:1150–1158.
44. Slankamenac K, Breitenstein S, Beck-Schimmer B, et al. Does pharmacological conditioning with the volatile anaesthetic sevoflurane offer protection in liver surgery? *HPB (Oxford)*. 2012;14:854–862.
45. Song JC, Sun YM, Yang LQ, Zhang MZ, Lu ZJ, Yu WF. A comparison of liver function after hepatectomy with inflow occlusion between sevoflurane and propofol anesthesia. *Anesth Analg*. 2010;111:1036–1041.
46. Golembiewski J. Economic considerations in the use of inhaled anesthetic agents. *Am J Health Syst Pharm*. 2010;67:S9–S12.
47. Weinberg L, Story D, Nam J, McNicol L. Pharmacoeconomics of volatile inhalational anaesthetic agents: an 11-year retrospective analysis. *Anaesth Intensive Care*. 2010;38:849–854.
48. Graham AM, Myles PS, Leslie K, et al. A cost-benefit analysis of the ENIGMA trial. *Anesthesiology*. 2011;115:265–272.
49. Spahn DR, Theusinger OM, Hofmann A. Patient blood management is a win-win: a wake-up call. *Br J Anaesth*. 2012;108:889–892.