Author's response to reviews

Title: Impact of Bleeding-related Complications and/or Blood Product Transfusions on Hospital Costs in Inpatient Surgical Patients

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Author's response to reviews: see over
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Re: Impact of Bleeding-related Complications and Blood Product Transfusions on Hospital Costs in Inpatient Surgical Patients

Dear Dr. Norton:

Please find attached our revised manuscript entitled “Impact of Bleeding-related Complications and Blood Product Transfusions on Hospital Costs in Inpatient Surgical Patients.” This letter provides point-by-point replies to each of the reviewers’ additional comments and how these have been addressed in the manuscript.

Thank you for the opportunity to publish this article in the BMC Health Services Research online journal and extending the deadline for this revision until February 28, 2011. We hope our responses to the reviewers’ comments and the changes made to our manuscript have adequately addressed the concerns regarding this study. If not, please do not hesitate to give me a call.

Sincerely,

Michael E. Stokes, MPH
MES:neb
Reviewer #1

Thanks for addressing all the issues I have raised in my review of your manuscript. However, include a table in the manuscript that summarizes the results of the regression analyses using GEE methods.

A table summarizing results of GEE models has been added to the manuscript (see table 6).

Text describing the GEE models have been added to the methods and results sections as follows:

Methods, Data Analyses section, page 10:

*Generalized estimating equation (GEE) models with a Gamma distribution and log link function were also used to measure the impact of bleeding-related complications and/or blood product transfusion events on total hospital costs while accounting for the effects related to the clustering of patients receiving care from the same hospitals. The same baseline parameters used for the ordinary least squares regression models of total hospital costs were included in GEE models.*

Results, page 14:

*Table 6 reports the ratio of average total costs for patients with bleeding-related complications versus those without bleeding-related complications, adjusted for differences in baseline and clinical characteristics and accounting for the effects related to the clustering of patients receiving care from the same hospitals using GEE models. Ordinary least squares modeling results are also presented for comparison. The ratio of average total costs estimated using GEE models for patients with bleeding complications vs. those without complications ranged from 1.31 to 1.93 for cardiac and vascular surgery, respectively and were all statistically significant. Cost ratios were similar to those observed using OLS regression with the exception of the ratio for general surgery (1.46 vs. 1.34 for GEE and OLS models, respectively).*

Reviewer #2

This study of hospital costs associated with post-operative bleeding complications/interventions is generally well-written, addresses an important issue and provides useful and interesting new data. The improved re-submission (especially the discussion) more than adequately addresses many issues raised in prior reviews. However, the analysis and presentation still raise some (generally addressable) issues. Specific comments follow, including those on some issues that appear to remain from the prior review.

Under the journal’s review criteria, it would appear mandatory that a revised manuscript would, at a minimum, explicitly address or comment on the bracketed (i.e., [ ]) issues raised below. This does not necessarily require that the analysis be redone.
ABSTRACT:

[[Assuming this is true, Results here should clarify that incremental cost differences were adjusted for covariates.]]

Abstract, page 3, we have revised the last sentence as follows:

The incremental cost per hospitalization associated with bleeding-related complications and adjusted for covariates… to address the reviewer’s comment

TEXT:

Introduction:

1st paragraph. Deaths from bleeding due to the trauma that precipitated admission are not as relevant to discussions of bleeding as a surgical complication as are deaths from bleeding that started during the surgery performed for trauma.

Materials and Methods:

1st paragraph: [[The authors should briefly describe the PCD (inclusion criteria for patient and provider populations, how hospitals are chosen, etc.).]]

Methods, Data source, page 5, we have added the following to clarify:

“The Premier healthcare alliance was formed for hospitals to share knowledge, improve patient safety, and to reduce risks. Participation in the Premier healthcare alliance is voluntary. The PCD is comprised of hospital administrative data from the United States and, although the PCD excludes federally-funded hospitals (e.g., Veterans Affairs), the hospitals included are nationally representative based on bed size, geographic location, and teaching hospital status [16]. Approximately 5 million new hospital discharges are added to the database each year. According to the Healthcare Utilization Project (HCUP) data, there were 39.5 million hospital discharges throughout the US in 2007. Therefore, the Premier data used at the time of this analysis represented approximately 13% of all US hospital discharges. All hospitals participating in the healthcare alliance submit data on all patients, payors, and providers as captured on the hospital billing record to Premier. The data go through quality assurance and validation checks and once the data have been validated the information is added to the database.”

Criteria and data sources for variables such as race (who report this?), geographic region, urban/rural status, etc. should be included and/or referenced. ]]

Methods, Data source, pg 6, we have added the following:

“Hospitals submit demographic data including patient reported race (White, Black, Hispanic, American Indian, Asian/Pacific Islander, Other). Data on hospital characteristics including hospital bed size, teaching hospital status (Yes/No), and hospital location (Urban/Rural) are reported by the hospitals. The geographic location of the provider (New England, Middle Atlantic, East North Central, West North Central, South Atlantic, East South Central, West South Central, etc.) should be included and/or referenced.”
Data from the AHRQ Healthcare Cost and Utilization Project indicate that there are more than 30 million discharges from US hospitals annually. Therefore the 5 million captured by PCD represent less than the stated one sixth of annual discharges from US hospitals (especially if one wishes to account for discharges from federal hospitals in the total denominator).

We have revised the Methods, Data Source section on page 5 to better estimate the proportion of US hospital discharges contained within Premier as follows using data from HCUP:

“Approximately 5 million new hospital discharges are added to the database each year. According to the Healthcare Utilization Project (HCUP) data, there were 39.5 million hospital discharges throughout the US in 2007. Therefore, the Premier data used at the time of this analysis represented approximately 13% of all US hospital discharges.”

Presumably the PCD has encrypted identifiers that allow multiple admissions for individual patients or admissions of different patients to the same hospital to be linked.

Because the patient and provider information contained within the PCD are de-identified we were able to gain access to the data without receiving approval from an IRB. Similarly, the organizations of the study authors also did not require approval from an IRB for using the data and conducting the study. Hence, IRB approval was not obtained. IRBs are governed according to Title 45 CFR Part 46 in the United States which states that exemptions to IRB approval include research activities in which the only involvement of human subjects was through research involving the collection or study of existing data, documents, records, etc, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

This document can be found at the following location:

http://ohsr.od.nih.gov/guidelines/45cfr46.html

Our study using the Premier data correctly fits into this exemption. We have modified the Methods, Data Source section, page 6 as follows to explain this better:

“Patient and provider information contained within the PCD are de-identified making it fully compliant with the Health Insurance Portability and Accountability Act privacy regulations. IRB approval for this study was not required as stated by Title 45 CFR (Code of Federal Regulations) Part 46 of the United States under the exemption that this research involved the study of existing data and that the information was recorded in such a manner that the subjects
could not be identified, directly or through identifiers linked to the subjects. Hence, IRB approval was not obtained.”

2nd paragraph: [[ It would appear that the ~5% of admissions with multiple procedures should have been categorized by the single most relevant procedure (based on some specified criteria) and then counted just once in the analysis, or excluded because of problems with determining which surgical procedure sub-group was most appropriate. It would appear that a re-analysis that does not count these cases (at least) twice should perhaps be performed. Admittedly this might only apply to (or change results for) surgical procedure sub-groups more affected by this double-counting. Please comment. ]]

Discussion, 8th paragraph, page 17: the following paragraph was added to examine the effect these patients with multiple procedures might have had on study results by excluding them:

“It should be noted that a small percentage of patients (approximately 5%) were included in more than one study subgroup because they were operated on in surgical sites spanning multiple surgical categories during the index hospitalization. A sensitivity analysis excluding these patients was conducted to examine the effect they might have had on cost results. Results show that their effect was minimal as the incremental difference in mean total costs (bleeding-related complication – no complication) were similar to the main analyses for each of the surgical subgroups (cardiac: $10,391, vascular: $14,639, non-cardiac thoracic: $12,366, solid organ: $12,434, general: $3,974, knee/hip replacement: $3,148, reproductive organ: $3,266, and spinal surgery: $17,448).”

[[That patients of all ages were included should be stated in the Methods section. It would appear that the different spectra of ages, procedures and co-variates seen in pediatric surgical cases *might* argue for separate analyses of such cases, or for including in the paper an explanation of why this was not done. ]]

Page 6, Patient Population section, 2nd sentence was added:

“Patients of all ages were included in this study” to make clear that pediatric patients were included in the main study results.

Lumping the pediatric surgical cases with the adult cases provides no insight regarding pediatric surgical cases and does not clarify the results for adults either.

We did lump the pediatric surgical cases with the adult cases for this analysis because our research question was to estimate bleeding-related costs for all patients not specifically just for adults and pediatric cases. However, since you have an interest in the differences in costs between adults and pediatric cases we have included the results of these sub-analyses in the discussion section, 7th paragraph, page 16:

“Third, pediatric patients <18 years of age were included in analyses. Although age was

included as a covariate in multivariate cost models, one could argue that, because pediatric
patients likely underwent different procedures compared to adult patients, separate analyses of these distinct patient groups is warranted. Thus, stratified analyses examining adult and pediatric patients separately were conducted to provide insight regarding the differences in costs between these two distinct subpopulations. Among adults, patients with bleeding-related complications had higher costs relative to patients without complications (Cardiac: $38,686 vs. $28,914, Vascular: $30,640 vs. $16,027, Non-cardiac thoracic: $36,150 vs. $23,494, Solid organ: $31,807 vs. $18,878, General surgery: $18,880 vs. $14,427, Knee/hip replacement: $18,248 vs. $15,247, Reproductive organ: $9,269 vs. $6,493, and Spinal: $37,978 vs. $20,847); results were similar to main analyses and statistically significant. Among the subset of pediatric patients, those with bleeding-related complications had higher costs relative to patients without complications (Cardiac: $58,239 vs. $29,514, Vascular: $113,822 vs. $39,506, Non-cardiac thoracic: $79,898 vs. $35,680, Solid organ: $61,122 vs. $28,742, General surgery: $104,505 vs. $37,316, Reproductive organ: $34,703 vs. $16,999, and Spinal: $54,369 vs. $31,984). A multivariate model was not created for pediatric knee/hip surgery patients because of the small sample size relative to the number of parameters in the model. Overall, costs in patients <18 years of age were higher compared to the adult population. The incremental difference in costs between patients with bleeding-related consequences and those without bleeding-related consequences was also much higher in pediatric patients compared to adults.”

3rd paragraph: [[Did the authors consider excluding vascular trauma, ruptured aortic aneurysm, GI bleeding, etc., from the study to facilitate excluding bleeding occurring as a consequence of the underlying or presenting condition?]]

Discussion section, 5th paragraph, page 16: The following text has been added to the end of the 5th paragraph to discuss this point:

“…it is possible that some patients within the bleeding-event and/or blood product transfusion group had a transfusion that did not occur as a consequence of the surgery and were misclassified. We did not exclude patients with conditions such as vascular trauma or ruptured aortic aneurysms from this analysis in order to facilitate bleeding occurring as a consequence of...
the surgery. Patients presenting with aortic aneurysms probably would have undergone either open aortic resection with replacement (38.44) or endovascular repair (39.71). The proportion of vascular surgery patients undergoing open aortic resection with replacement was only 1.8% and patients undergoing endovascular repair were not selected for this analysis. Therefore, we do not expect the inclusion of patients with ruptured aortic aneurysm and the possible misclassification of the bleeding outcome to change results significantly. With respect to vascular trauma, the inclusion of trauma cases who likely had a transfusion as a result of their presenting condition and not the surgical procedure likely introduced some misclassification bias into this study. Since trauma patients have much higher costs relative to patients without trauma, the inclusion of these cases likely would have had the effect of inflating our bleeding-related complication cost estimates [21]. We suspect that this upward bias is probably minimized by the fact that patients presenting with trauma probably represented only a small percentage of the total patients included in this study. A study from the University of Michigan comparing outcomes between trauma and general surgery patients reported enrolling only 525 patients admitted to the Trauma service in comparison to 54,478 general surgery patients during 2004 [21]."

5th paragraph: The term prior hemostat exposure might better be described as pre-operative use of substances that promote hemostasis if that is what was meant. ORC should be spelled out.

Methods section, 5th paragraph, page 9: The text was changed as follows to address the above comment:

“Pre-operative use of substances that promote hemostasis was defined as receipt of a hemostat in any of the hemostat classes including oxidized regenerated cellulose, collagen, gelatin, fibrin sealant, thrombin, flowables, combination products, and adhesion prevention.”

Prior hemostat exposure was changed to “pre-operative use of substances that promote hemostasis” in the results and tables sections as well.

Results

Results in the text should emphasize that incremental LOS differences were unadjusted for covariates. Age ranges are not in Table 3.

Results section, 5th paragraph, page 12: The following text has been added to the end of the paragraph, making this point more clear:

“Lengths of stay differences were unadjusted for covariates.”

Tables section, Table 3, page 29: Age range has been added to Table 3

[[For each surgical procedure subgroup, the % of cases < 18 years old should at least be noted. For each surgical procedure subgroup, the % of cases counted twice somewhere in the analysis should also at least be noted.]]
Results section, 3rd paragraph, page 11: The following text has been added to the end of this paragraph to make note of the percentage of patients <18 years old and the percentage of patients included in multiple surgical subgroups for each of our surgical subgroups:

“Patients less than 18 years of age were included in this study and represented 2.5%, 1.2%, 4.6%, 3.7%, 2.6%, 0.03%, 0.9%, and 2.2% of patients in the cardiac, vascular, non-cardiac thoracic, solid organ, general, knee-hip replacement, reproductive organ, and spinal surgery subgroups, respectively (data not shown). It was possible for some patients to be operated on in surgical sites spanning multiple surgical categories during the index hospitalization. These patients accounted for 15.5%, 15.1%, 20.2%, 41.8%, 11.3%, 1.0%, 3.2%, and 5.1% of patients in the cardiac, vascular, non-cardiac thoracic, solid organ, general, knee-hip replacement, reproductive organ, and spinal surgery subgroups, respectively (data not shown).”

Competing Interests

As this study was entirely industry-funded, the companies involved (United BioSource, Ethicon and Excenda) should be briefly described. [[ The existence of any products potentially relevant to the study should be briefly noted in the manuscript. For example, it would be useful for readers to know if any of these companies make or support companies that make products that prevent or reduce bleeding complications, since they could benefit directly or indirectly from results showing larger costs attributable to such complications.]]

We have modified the second half of the Competing Interests section, pg. 21 to make known to readers that Ethicon manufactures and markets products designed to achieve adjunctive hemostasis and to better describe the relationship between Ethicon and UBC and Ethicon and Excenda. Please see the bolded changes to the statement below:

“United BioSource Corporation is a global scientific and medical affairs organization that partners with life science companies to help generate real-world evidence of product effectiveness, safety, and value to assist health care decisions and enhance patient care. Ethicon Inc. is a global medical device company with major products covering wound closure; hernia repair; biosurgery; women’s health, aesthetic medicine and ENT. It develops, manufactures and markets a variety of products designed to achieve adjunctive hemostasis. Excenda is a full-service consultancy and managed markets agency that helps manufacturers identify, demonstrate, and deliver their brand’s value proposition to healthcare stakeholders. UBC and Excenda are independent consulting firms that were contacted by Ethicon to perform this study.”