Bachelor of Science in Medicine Degree Program
End of Term Final Report

Student Name: Prabjot Singh **Date:** 07/31/18

Project Title: The risk of febrile morbidity following massive intraoperative blood loss during gynecologic laparotomy among oncology patients.

Primary Supervisor Name: Alon Altman
Department: Obstetrics, Gynecology and Reproductive Sciences

Co-Supervisor Name: Erin Dean
Department: Obstetrics, Gynecology and Reproductive Sciences

Summary (250 words max single spaced):

Objective:To investigate the relationship between massive intraoperative blood loss (MIBL) and postoperative infection in gynecologic laparotomies of oncology patients.

Methods:We performed a retrospective cohort study of all gynecologic laparotomies for oncologic indications at a tertiary care center, between 2012 and 2016. Only patients who had a laparotomy for gynecologic oncology indications were included in this study. Criteria for cases of MIBL (n=169) were: > 1 liter of blood loss operatively, > 40 g/L drop in hemoglobin by postoperative day one, or perioperative blood transfusion. Every third chart that did not meet criteria for MIBL was selected as a control (n=226). The primary outcome was defined as a positive wound swab culture, positive urine culture or criteria for systemic inflammatory response syndrome. We collected data on BMI, age, type and indication for surgery, complications and comorbidities to investigate potential confounders.

Results:The incidence rate of the primary outcome was 46.8% for MIBL and13.3% for the non-MIBL group ($p<0.0001$). Mean age was 58.9 ± 13.1 years for cases of MIBL and 59.5 ± 12.5 years for controls. Mean BMI was 28.2 kg/m^2 ± 7.2 kg/m^2 for cases and 33.4 ± 9.4 kg/m^2 for controls (<0.0001). The adjusted odds ratio for risk of primary outcome for cases of MIBL versus controls is 5.403 (95% CI 3.25-8.99, $p<0.0001$).

Conclusion:MIBL is associated with an increased risk of post-operative febrile or infectious morbidity in gynecology oncology patients. This data supports the rationale for additional prophylactic antibiotics in cases of MIBL.

Student Signature
Digitally signed by Prabjot Singh
Date: 2018.07.29 10:37:26 -05'00'

Primary Supervisor Signature
Alon Altman
Digitally signed by Alon Altman
Date: 2018.07.31 18:27:15 -05'00'

Acknowledgments: I gratefully acknowledge the sole or partial funding support from the following sponsors;

H.T. Thorlakson Foundation
Dean, College of Medicine
Research Manitoba

Manitoba Medical Service Foundation (MMSF)
Vice-Dean, Research Rady FHS
Health Sciences Centre Research Foundation
Heart and Stroke Foundation

Sponsorship if different than above;
Additionally- The University of Manitoba Students' Union Travel Grant

Introduction

Infections occurring after gynecologic surgery are a major source of morbidity and mortality. Some common infections include urinary tract infections, endometritis, wound infection, vaginal cuff cellulitis, perineal infection and sepsis.(1) These infections can lead to prolonged hospital stays and increased health care cost. A study conducted by Roy et al. found that readmission rates for gynecologic surgery are tripled due to surgical site infections, cost is doubled, and length of stay is tripled compared to patients who did not have surgical site infections.(2) Reducing the incidence of postoperative infections would not only translate to better patient outcomes, but also to significant cost savings.

It is accepted that massive intraoperative blood loss (MIBL) is a risk factor for post-operative infection with little evidence supporting this association. The few studies conducted have found an association between MIBL and post-operative febrile morbidity specifically in liver transplantation and radical hysterectomy and pelvic lymphadenectomy.(3,4) The only study investigating gynecology oncology patients found that MIBL was the only significant predictor for postoperative febrile morbidity, however this study was limited to patients with FIGO stage IB-IIA cervical cancers undergoing radical hysterectomy and pelvic lymphadenectomy.(4)

The predisposition to infection due to massive intraoperative blood loss has many proposed mechanisms including diminished delivery of oxygen to end organs resulting in end-organ dysfunction(5), diminished delivery of oxygen to the wound, dilution effects of fluid and blood loss on antibiotics given prophylactically and diminished delivery of essential factors and cells involved in wound healing and repair.(6)

The current guidelines from the Society of Obstetrics and Gynaecology of Canada recommend giving an additional dose of prophylactic antibiotics if the procedure is >3 hours long or if the estimated blood loss is greater than 1,500ml.(1) This is a IIIC recommendation indicating that it is based on a poor level of evidence and emphasizes the need for further research into the association between MIBL and post-operative febrile morbidity, especially in gynecologic oncology procedures. There is also no literature on the effects of age(7,8), BMI(9–12) and diabetes(9,10,13) on postoperative febrile morbidity.

Our group previously investigated rates of MIBL and post-operative febrile morbidity at our institution and reported the first baseline rates of MIBL for open gynecologic surgeries (13.5%) and subsequent postoperative febrile morbidity (26%).(6) In this study, we reviewed cases of gynecologic oncology patients, between the ages of 18-90, who have undergone gynecologic laparotomies to determine whether MIBL is independently associated with increased risk of post-operative infectious morbidity.

Methods

We performed a retrospective cohort study of all gynecologic laparotomies at the Health Sciences Center, Winnipeg, Manitoba, between 2012 and 2016. Only patients who had a laparotomy for gynecologic oncology indications were included in this study.

Criteria for cases of MIBL (n=169) were: > 1 liter of blood loss operatively, > 40 g/L drop in hemoglobin by postoperative day one, or perioperative blood transfusion. Every third chart that did not meet criteria for MIBL (non-MIBL) was selected as a comparison (n=226) (Figure 1).

Once a case of MIBL or non-MIBL was identified, a full chart review was conducted. We collected data on type of procedure, age, BMI, medications used, comorbidities, lifestyle factors,

indications for surgery, urgency of surgery, length of procedure, booking temperature, lowest intra-operative temperature, prophylactic antibiotic therapy (time of administration, type, dose, other antibiotics used intraoperatively), skin prep, type of incision, intraoperative fluids used (type and amount), surgical complications, drains left *in situ*, blood transfusion required and our primary and secondary outcomes. These potential pre-operative and intraoperative covariates are listed in Table 1 and Table 2.

The primary outcome was defined as a positive wound swab culture, positive urine culture or criteria for systemic inflammatory response syndrome (temperature >38°C or <36°C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute or arterial carbon dioxide tension [PCO2] <32 mmHg, abnormal white blood cell count [>12 000/μL or <4000/μL]). The secondary outcomes were: readmission, reoperation, clinical description of a wound infection, postoperative antibiotic prescription or isolated fever.

Pairwise relationships between the primary and secondary outcomes and MIBL, and between MIBL and the potential covariates were tested using the chi-square tests between two categorical variables and the Wilcoxon rank tests between one categorical variable and one continuous variable. The covariates were selected using a stepwise method. Logistic regression was used for the relationships between MIBL and the composite primary outcome with the adjustments for the covariates. Statistical analysis was performed using SAS (v9.3).

Results

The incidence rate of the primary outcome (febrile morbidity) was 46.8% for MIBL and13.3% for non-MIBL ($p<0.0001$) (Figure 1).

Table 1 and Table 2 indicate all of the potential pre-operative and intraoperative covariates. Of those variables, bowel injury, drains left *in situ*, vascular injury, surgical complications (Any) and mean BMI were found to be statistically significantly associated with MIBL. The mean age for cases of MIBL was 58.9 years ± 13.1 (Range 22-90) while the mean age for controls was 59.5 ± 12.5 (Range 20-83) ($p=0.5475$). The mean BMI for cases was 28.2 kg/m^2 ± 7.2 while the mean BMI for controls was 33.4 kg/m^2 ± 9.4 ($p<0.0001$). The remaining variables are comparable between the MIBL and non-MIBL groups. The statistically significant covariates associated with the exposure were incorporated into the statistical analysis.

Figure 2 shows the pairwise comparisons of the frequencies of the primary and secondary outcomes by MIBL status. All primary and secondary outcomes are statistically significantly higher in the MIBL group than in the non-MIBL group except for reoperation and post-operative febrile morbidity.

The odds ratio for risk of primary outcome for cases of MIBL versus non-MIBL is 5.40 (95% CI 3.25-8.99, $p<0.0001$) when controlling for the covariates (i.e. surgical complications to the bowel) after stepwise selection. This means oncology patients who meet criteria for MIBL are 5.4 times more likely to have febrile or infectious morbidity than the non-MIBL group.

Discussion

Massive intraoperative blood loss is independently associated with an increased risk of post-operative febrile or infectious morbidity in gynecologic oncology laparotomies. This means that gynecology oncology patients with massive intraoperative blood loss, defined as > 1 liter of blood loss operatively, > 40 g/L drop in hemoglobin by postoperative day one, or perioperative blood transfusion, are more likely to suffer from infectious morbidity.

Our results support the findings from the study conducted by Kietpeerakool et al. (2004) looking at patients with FIGO stage IB-IIA cervical cancers and radical hysterectomy and pelvic lymphadenectomy. They performed a logistic regression test adjusting for three significant covariates including preoperative anemia, operative time and estimated blood loss. They found that MIBL (>1500mL) was the only significant predictor for postoperative febrile morbidity with an odds ratio of 2.7 (95% CI 1.1-6.6, p=0.028).(4) A study conducted by Kaido et al. (2012) looking at liver transplantation patients found MIBL (>10L) to be one of the three independent risk factors for postoperative infectious complications with an odds ratio of 2.983 (95% CI 1.229-7.541, p=0.018)(3). Among out population of gynecologic oncology patients, we saw a strong association even when arguably lower threshold for MIBL was used (1000mL).

Limitations of this study include that it is a retrospective study. This means that other confounding factors may not have been documented or controlled for in the final model (for instance, exact preoperative hemoglobin levels). Further

- Composite outcome → under-powered to look at specific outcomes like wound infection independently
- Only looked for outcomes that occurred in the hospital – did not consider differences for outcomes that may have occurred in the outpatient setting (e.g. superficial/minor wound infections)

Our study provides further evidence for the independent association between MIBL and postoperative febrile morbidity in gynecology oncology patients, and further informs the current recommendation to prescribe an additional dose of antibiotics to patients experiencing MIBL. While adding a second dose of prophylactic antibiotics may reduce the postoperative infection risk for individuals with MIBL, there is currently no available evidence to demonstrate the efficacy of this management strategy.

Further avenues to explore include how much the risk of febrile morbidity is reduced after adding an additional dose of prophylactic antibiotics to patients who meet criteria for MIBL and what other interventions can reduce the risk of febrile morbidity in MIBL patients. Our group is planning to investigate this research question using a prospective study design that would allow further exploration into the mechanism behind this association.

Infectious morbidity has a large impact on patient morbidity, mortality and health care costs (6). Identifying strategies to reduce infectious morbidity will allow us to improve patient care and reduce health care costs. This study provides evidence that massive intraoperative blood loss is an independent predictor of postoperative febrile or infectious morbidity among a broad group of gynecologic oncology patients. This opens the door to further research into this topic in hopes to provide information for appropriate prophylaxis strategies and to improve patient outcomes.

References

1. Van Eyk N, van Schalkwyk J, Yudin MH, Allen VM, Bouchard C, Boucher M, et al. Antibiotic Prophylaxis in Gynaecologic Procedures. J Obstet Gynaecol Canada [Internet]. 2012;34(4):382–91. Available from: http://dx.doi.org/10.1016/S1701-2163(16)35222-7

2. Roy S, Patkar A, Daskiran M, Levine R, Hinoul P, Nigam S. Clinical and Economic Burden of Surgical Site Infection in Hysterectomy. Surg Infect (Larchmt) [Internet]. 2014;15(3):266–73. Available from: http://online.liebertpub.com/doi/abs/10.1089/sur.2012.163

3. Kaido T, Mori A, Ogura Y, Ogawa K, Hata K, Yoshizawa A, et al. Pre- and perioperative factors affecting infection after living donor liver transplantation. Nutrition. 2012;28(11–12):1104–8.

4. Kietpeerakool C, Lattiwongsakorn W, Srisomboon J. Incidence and predictors of febrile morbidity after radical hysterectomy and pelvic lymphadenectomy for early stage cervical cancer patients. Asian Pac J Cancer Prev [Internet]. 2008;9(2):213–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18712961

5. Purvis TE, Goodwin CR, Molina CA, Frank SM, Sciubba DM. Spine Surgery Patients. 2018;28(March):345–51.

6. Leylek M, Poliquin V, Al-Wazzan A, Dean E, Altman AD. Postoperative Infection in the Setting of Massive Intraoperative Blood Loss. J Obstet Gynaecol Canada [Internet]. 2016;38(12):1110–3. Available from: http://dx.doi.org/10.1016/j.jogc.2016.09.010

7. Yazici Y. Immune Function in older adults. 2017;1–23.

8. Weiskopf D, Weinberger B, Grubeck-Loebenstein B. The aging of the immune system. Transpl Int. 2009;22(11):1041–50.

9. Pitts SI, Maruthur NM, Langley GE, Pondo T, Shutt KA, Hollick R, et al. Obesity, Diabetes, and the Risk of Invasive Group B Streptococcal Disease in Nonpregnant Adults in the United States. Open Forum Infect Dis [Internet]. 2018;5(6):2011–2. Available from: https://academic.oup.com/ofid/article/doi/10.1093/ofid/ofy030/5034833

10. Langley GE, Pondo T, Harrison L, Farley MM, Lindegren M Lou, Nichols M, et al. obesity and diabetes on group a strep. 2018;1(July):2339155.

11. Falagas ME, Kompoti M. Obesity and infection. Lancet Infect Dis. 2006;6(7):438–46.

12. Francis D Sheski M. Overweight and obesity in adults: health consequences. 2018;(figure 1):17–9.

13. Francis D Sheski M. Susceptibility to infections in persons with diabetes. 2018;17–9.

Tables and Figures

Figure 1. Bird's eye view of the individuals used in this study

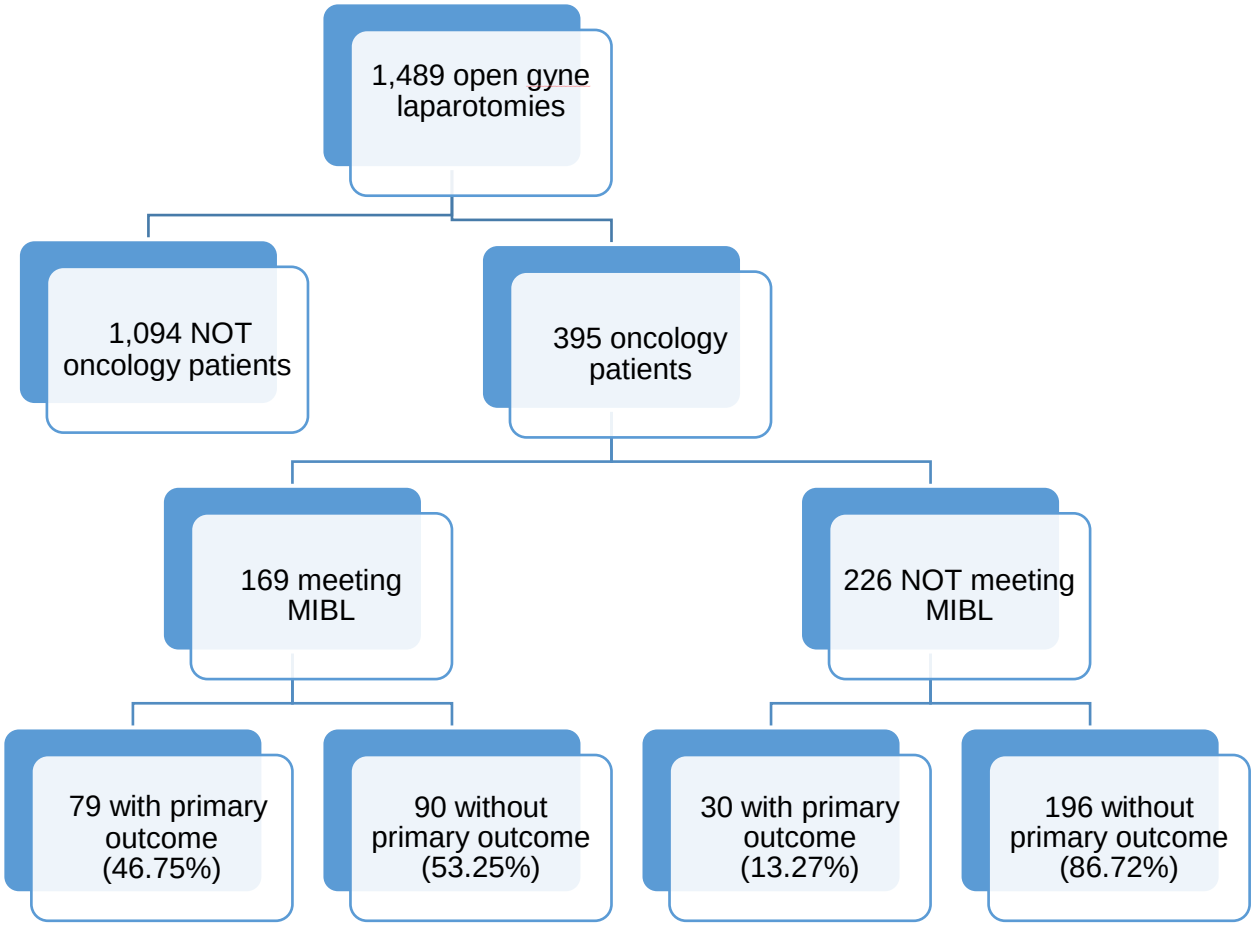

Figure 2. Pairwise comparisons of the frequencies of the primary and secondary outcomes by the MIBL status. *p value 0.01-0.05, **p value 0.001-0.01, *** p value<0.001, NS: not significant.

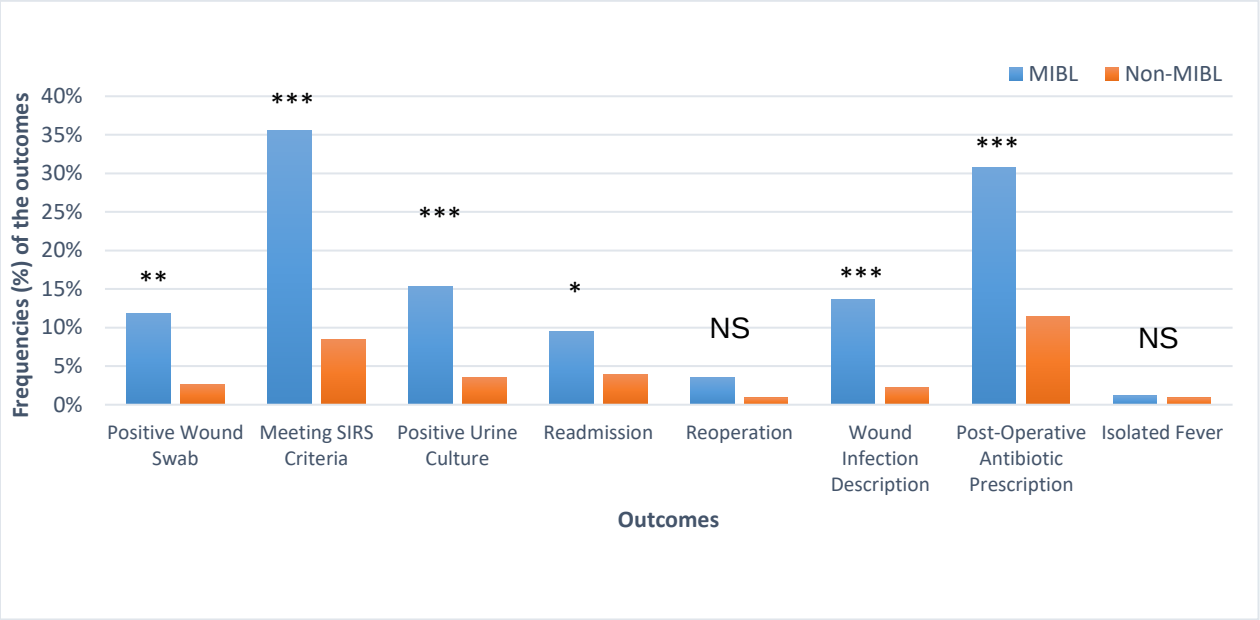

Table 1: Potential preoperative covariates and their relationships with MIBL

Variable		MIBL (n=169)	Non-MIBL (n=226)	p-value
Diabetes				0.5881
	Y	30 (17.8%)	45 (19.9%)	
	N	139 (82.3%)	181 (80.1%)	
Immunosuppression				0.2591
	Y	26 (15.4%)	26 (11.5%)	
	N	143 (84.6%)	200 (88.5%	
Smoking				0.1863
	Y	34 (20.1%)	34 (15.0%)	
	N	135 (79.9%)	192 (85%)	
Mean BMI				<0.0001
		28.2 kg/m^2 ± 7.2	33.4 kg/m^2 ± 9.4	
Mean Age				0.5475
		58.9 ± 13.1 years	59.5 ± 12.5 years	

Table 2: Potential intra-operative covariates and their relationships with MIBL

Variable		MIBL (n=169)	Non-MIBL (n=226)	p-value
Bowel Injury				0.0015
	Y	20 (11.8%)	8 (3.5%)	
	N	149 (88.2%)	218 (96.5%)	
Vascular Injury				0.0418
	Y	8 (4.7%)	3 (1.3%)	
	N	161 (95.3%)	223 (98.7%)	
Bladder Injury				0.7694
	Y	2 (1.2%)	2 (0.9%)	
	N	167 (98.8%)	224 (99.1%)	
Surgical Complications (Any)				<0.0001
	Y	33(19.5%)	14 (6.2%)	
	N	136 (80.5%)	212 (93.8%)	
Urgency of the OR				0.6593
	Elective	167 (98.8%)	223 (98.7%)	
	Urgent	2 (1.2%)	2 (0.9%)	
	Emergent	0 (0%)	1 (0.4%	
Incision Type				0.9987
	Midline	142 (87.1%)	196 (87.1%)	
	Pfannensteil	21 (12.9%)	29 (12.9%)	
Drains left in situ				0.0014
	Y	25 (14.8%)	12 (5.3%)	
	N	144 (85.2%)	214 (94.7%)	