RESEARCH COMMUNICATION

Incidence and Predictors of Febrile Morbidity after Radical Hysterectomy and Pelvic Lymphadenectomy for Early Stage Cervical Cancer Patients

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Abstract

This study was undertaken to evaluate the incidence and independent predictors for febrile morbidity after radical hysterectomy and pelvic lymphadenectomy. Patients with FIGO stage IB-IIA cervical cancers who had undergone RHPL at Chiang Mai University Hospital between January 2003 and December 2005, were reviewed. The clinical variables including the age at diagnosis, menopausal status, body mass index, previous cervical conization, tumor size, preoperative chemotherapy, preoperative anemia, operative time, and estimated blood loss were analyzed for prediction of postoperative febrile morbidity. During the study period, 357 women were reviewed. The mean age was 44.7 years. Sixty-five (18.2%) women were postmenopausal. The majority of women (77.3%) were in FIGO stage IB1. The most common histology was squamous cell carcinoma (69.2%). Febrile morbidity was noted in 94 women (26.3%, 95% CI= 21.8-31.2) in whom 25 (7.0%) had urinary tract infection (19), abdominal wound infection (4), and vaginal cuff infection (2), respectively. Only massive blood loss (>1,500 ml) was noted as the significantly independent predictor for febrile morbidity (aOR= 2.7, 95% CI=1.1-6.6, P=0.028). In conclusion, approximately one-fourth of the women undergoing RHPL at our institute had postoperative febrile morbidity. Only massive blood loss is a significant predictor for this complication.

Key Words: Radical hysterectomy - pelvic lymphadenectomy - febrile morbidity -complications

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Introduction

Radical hysterectomy and pelvic lymphadenectomy (RHPL) are considered to be the standard surgical treatments for patients with FIGO stage IB-IIA cervical cancer. Landoni et al reported the 5-year overall survival rate and disease free survival rate in patients, who had undergone RHPL were 83% and 74%, respectively (Landoni et al., 1997). Although these favorable outcomes were identical in those who received pelvic radiation as the primary treatment, the possible benefits gained from RHPL includes the ability to preserve ovarian function particularly in young patients, less sexual dysfunction, and a shorter time interval from diagnosis to completion of treatment. In our institute, approximately 120 RHPLs were carried out each year (Suprasert et al., 2005).

The complications following RHPL generally fell into three categories: acute, sub-acute, and chronic complications. In acute complications, the most common cause was febrile morbidity ranging widely from 20% to 70% (Boyce et al., 1981; Sevin et al., 1984; Marsden et al., 1985; Micha et al., 1987; Hemsell et al., 1989; Orr et al., 1990; Sevin et al., 1991; Maleemonkol et al., 1998). Because of the considerably high incidence of this complication, it would be beneficial to know which patients are at a higher risk. The authors chose to evaluate febrile morbidity rather than infectious morbidity because only fever can increase hospital stay and cost. Accordingly, this study was undertaken to evaluate the incidence and the significant predictors for febrile morbidity after RHPL for stage IB-IIA cervical cancer patient in our institute. These will provide the surgeon with the important information for consideration of appropriate surgical technique, prophylactic strategies, and patient's counseling before operation.

Materials and Methods

Patients with FIGO stage IB-IIA cervical cancer undergoing RHPL at Chiang Mai University Hospital between January 2003 and December 2005, were retrospectively analyzed. Abstract data included the age at operation, body mass index (BMI), menopausal status, FIGO staging, previous cervical conization, greatest dimension of tumors, preoperative anemia, amount of intraoperative blood loss, operative time, blood transfusion, postoperative anemia, and perioperative complications.

RHPLs were performed by a gynecologic oncologist with a fellow. The abdomen and vagina were immediately prepared with Betadine before operation. A Foley catheter was inserted and maintained for 7 days postoperatively.

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Self intermittent bladder catheterization was then advised for women who had residuals greater than 50-100 ml. Extraperitoneal drainage was not routinely carried out.

One gram of ampicillin was given intraveneously 30 minutes before operation and was continued every 6 hours after the operation for the first 2 days, followed by 500 mg of amoxicillin given orally four times a day. In total, antibiotics were given for 7 days postoperatively.

Fever was defined as a temperature of 38.0°C that occurred in any two of the first 10 days postoperation, excluding the first 24 hours, taken by mounth by a standard technique at least four times daily. Specific postoperative infection was diagnosed by clinical symptoms and signs and/or laboratory tests.

The statistical analysis was carried out using SPSS computer software (SPSS Inc, Chicago, Ill). Descriptive statistics were used for demographic baseline data. The chi-square or Fisher exact test were used to univariately identify factors related to the presence of febrile morbidity. For those factors with a P value of less than 0.25 in univariate analysis, a multivariate analysis using logistic model was further used to find the independent factors. An odds ratio, with a 95% confidence interval that did not include unity, was considered statistically significant. This study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University.

Results

During the study period, 357 women who matched the study inclusion were reviewed. The mean age was 44.7 years (median, 44; range, 27-73). Sixty-five (18.2%) women were postmenopausal and all did not concurrently receive hormonal replacement therapy. Fifty-two (14.6%) women had tumor size of greater than 4 cm at its greatest diameter. Three hundred and two women (84.6%) underwent low midline abdominal incisions; the remaining 55 (15.4%) underwent Maylard incisions.

Due to the long waiting period from the diagnosis to operation, 129 (36.1%) women received preoperative single cisplatin at a dose of 75 mg/m2 for 1-2 cycles depending on their extent of waiting time. Eighteen (5.0%) women had preoperative anemia. None had preoperative radiation. Table 1 displays the frequency of FIGO stage, histologic types, previous cervical conization, and high-risk pathologic factors after RHPL in this study.

The febrile morbidity after RHPL was noted in 94 (26.3%; 95% confidence interval [CI], 21.8 % to 31.2 %), in whom 25 (7.0%; 95% CI, 4.6% to 10.2%) had urinary tract infection (19), abdominal wound infection (4), and vaginal cuff infection (2), respectively.

Univariate analysis, which included the age at diagnosis, menopausal status, body mass index, previous cervical conization, tumor size, preoperative chemotherapy, preoperative anemia, operative time, and estimated blood loss was performed. Preoperative anemia, long operation time, and massive blood loss were found to have a P-value of less than 0.25. Multivariate analysis using logistic regression model which included the remaining 3 significant covariates including , preoperative anemia, operative time and estimated blood loss, was then performed. Only massive blood loss of greater than 1,500 ml remained a statistically significant predictor for febrile morbidity after RHPL. Women who experienced massive blood loss during the operation had 2.7 times the risk of having febrile morbidity (Table 2).

Table 1. Clinicopathologic Characteristics

Characteristics	Number	(percentage)
FIGO stage		
IB1	276	(77.3)
IB2	45	(12.6)
IIA	36	(10.1)
Histologic types		
Squamous cell carcinoma	247	(69.2)
Addenocarcinoma	88	(24.6)
Others	22	(6.2)
Previous conization		
None	274	(76.8)
LEEP	66	(18.5)
CKC	17	(4.8)
Parametrial invasion	23	(6.4)
Pelvic node metastasis	52	(14.6)
Vaginal margin involvement	23	(6.4)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LEEP, loop electrosurgical excision procedure; CKC, cold-knife conization.

Discussion

Generally, febrile morbidity after surgery may be due to the following 3 causes including surgical site infection, non-surgical site infection, and unexplained. For RHPL, there is a much greater risk of having febrile morbidity

Table 2. Univariate and Multivariate Analyses for Prediction of Febrile Morbidity

Variables/Category	No (%)	Univariate P-value	Multivariate OR (95%CI)	Multivariate P-value
Estimate blood loss				
>1,500ml	12/23 (52.2)	0.004	2.7 (1.1-6.6)	0.028
≤1,500ml	82/252 (32.5)			
Preoperative anemia				
Yes	8/18 (44.4)	0.073	2.1 (0.8-5.6)	0.144
No	86/339 (25.4)			
Operative time				
>4 hours	27/72 (37.5)	0.016	1.6 (0.9-2.9)	0.090
≤4 hours	67/285 (23.5)			
Age (years)				
> 50	19/71 (26.8)	0.927	Variable removed	
≤ 50	75/286 (26.2)			
Menopausal status				
Post-	16/65 (24.6)	0.728	Variable removed	
Pre-	78/292 (26.7)			
Body mass index				
> 30	5/23 (21.7)	0.683	Variable removed	
≤ 30	89/334 (26.6)			
Previous conization				
Yes	20/83 (24.1)	0.598	Variable removed	
No	74/274 (27.0)			
Tumor size (largest diameter)				
> 4 cm	15/52 (28.8)	0.656	Variable removed	
≤ 4 cm	79/305 (25.9)			
Preoperative chemotherapy				
Yes	31/129 (24.0)	0.458	Variable removed	
No	63/228 (27.6)			

than after a simple hysterectomy because of a more extensive operation, longer operative time, higher volume of blood loss, and longer bladder catheterization. In this study, the incidence of febrile morbidity following RHPL was 26.3%, in which 5.3% and 1.7% were non-surgical and surgical site infection, respectively. These results are consistent with the existing literature (Boyce et al., 1981; Sevin et al., 1984; Marsden et al., 1985; Micha et al., 1987; Hemsell et al., 1989; Orr et al., 1990; Sevin et al., 1991; Maleemonkol et al., 1998).

In this study, the authors systematically evaluated the demographic and operative characteristics to determine the relationship between febrile morbidity and RHPL. A logistic regression analysis revealed that only massive blood loss (>1,500 ml) during operation was a significant independent predictor for this complication. Women who experienced massive blood loss had 2.7 times the risk of having febrile morbidity after RHPL. Our finding is similar to that reported by Peipert et al(2004), which demonstrated that an increased blood loss at the time of hysterectomy significantly increases the risk of febrile morbidity. The significant effect of massive blood loss on febrile morbidity is theoretically plausible because a rapid clearance of the prophylactic antibiotics would be expected in cases with a high volume of blood loss, resulting in a suboptimal drug level. Therefore, the benefit of antibiotic prophylaxis would be diminished. Based on this finding, a repeat dose of prophylactic antibiotic should be considered in women experiencing massive blood loss during operation in order to maintain the therapeutic level of these prophylactic antibiotics.

Operative time is generally found to be an independent predictor of postoperative febrile morbidity(Guaschino et al., 2002). In this study, prolonged operative time of greater than 4 hours was a marginally significant predictor for post-RHPL febrile morbidity (aOR, 1.6; 95% CI, 0.9-2.9). The lacking of predictive significance of this variable in this study may due to the small study size. Although there is no standard definition of prolonged operative time for RHPL, the authors categorized an operative time of longer than 4 hours as prolonged operative time for RHPL because the prophylactic antibiotics used in the author's institution was ampicillin, which has a half-life of approximately 1.5-2 hours. Therefore, an operative time of greater than 2 times the half-life of antibiotics may increase the risk of febrile morbidity, because the prophylactic effect of the antibiotic may be loss due to its sub-therapeutic level. The administration of a repeat dose of prophylactic antibiotics in order to restore its therapeutic level, should be considered.

Several randomized controlled studies have demonstrated that prophylactic antibiotics reduce postoperative infections after RHPL (Rosenshein et al., 1983; Sevin et al., 1984; Marsden et al., 1985; Micha et al., 1987; Hemsell et al., 1989; Orr et al., 1990; Sevin et al., 1991). Due to the various antibiotics drug and regimens examined, a definite conclusion about the superiority of each drug and route could not be made. However, using longer duration antibiotics have no additional benefit compared to shorter duration (Orr et al., 1990; Sevin et al., 1991; Maleemonkol et al., 1998).

In the author's institution, since a Foley catheter was maintained for 7 days postoperatively, antibiotics administration was also extended to 7 days postoperatively in order to be a urinary tract prophylaxis. However, the benefit of this practice is still unclear and should be evaluated in prospective randomized controlled study for a definite conclusion.

This study was hampered by a number of limitations. First, this study was retrospective in nature. Therefore, the authors were limited to the variables collected in patient charts, and there may be other important risk factors for the incidence of febrile morbidity after RHPL. Second, the predictive significance of some variables may be underestimated due to the limitation of the study population.

In conclusion, approximately one-fourth of women undergoing RHPL experienced febrile morbidity. Only massive blood loss during operation was a significant independent predictor for such a complication. A repeat dose of prophylactic antibiotics in cases with massive blood loss therefore should be considered to maintain therapeutic drug levels.

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