RESEARCH COMMUNICATION

Lack of Effect of Perioperative Blood Transfusion during Radical Hysterectomy with Lymph Node Dissection on the Prognosis of Cervical Cancer Stage Ib

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Abstract

The aim of this retrospective study was to analyze the effects of perioperative blood transfusion during radical hysterectomy with lymph node dissection on the prognosis of cervical cancer stage Ib. A total of 295 patients who had undergone surgery from 1987-2002 were included. Forty seven patients underwent conization before definite surgery, and 2 patients were subsequently lost to follow up. Among the remaining 246 patients, 97 received allogenic blood transfusion, 38 received autologous blood transfusion, and 111 received no transfusion. The clinicopathologic finding of these three groups were reviewed and analyzed. There was no significant difference among three groups in age, chief complaints, duration of symptoms, size of lesion, histopathology, grade, margin or parametrium involvement, node status or postoperative adjuvant treatment. The most prominent presenting symptoms were abnormal vaginal discharge, abnormal vaginal bleeding, and postcoital bleeding. Although the 5-year disease-free survival (DFS) (and 95% CI) for autologous blood transfused group was 90.9% (74.4-97.0%), falling to 88.1% (77.8-93.8%) in untransfused blood group and 81.7% (71.3-88.6%) in allogenic transfused blood group, there were no significant differences among three groups (P = 0.699). In multivariate analyses, only age (P = 0.046), size of lesion (P = 0.024) and histology (P = 0.046) were statistically significantly associated with DFS, whereas transfusion status was not. In conclusion, there is no evidence that perioperative blood transfusion affects DFS of patients undergoing radical hysterectomy and pelvic lymphadenectomy. Only age, size of lesion and histology were statistically significantly associated with DFS.

Key Words: Cervical cancer - blood transfusion - prognosis

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Introduction

Cervical cancer is currently one of the most common female malignancies worldwide. In Thailand, it was the first leading cancer among females with approximately 6268 new cases each year (Sriplung et al., 2003). Early stage cervical cancer may be effectively treated with either surgery via radical hysterectomy with pelvic node dissection or radiation with or without concurrent chemoradiation. Radical hysterectomy with pelvic lymph node dissection was the accepted primary treatment for International Federation of Gynecology and Obstetrics (FIGO) stages I and IIa cervical cancer (Creasman et al., 1986). The main morbidities of radical hysterectomy with pelvic lymph node dissection were injury to great vessels, ureter, bladder, nerve and bowel (Bosze et al., 1993; Zorlu et al., 1998). Hemorrhage was the most common complication in this procedure, often requiring perioperative blood transfusion (Bosze et al., 1993).

In 1973, Opelz et al. reported that the use of blood transfusion enhanced renal allograft survival based on transfusion-induced immunosuppression (Opelz et al., 1973). In the 1980s Gantt was the first to predict an adverse effect of blood transfusion in cancer patients as a consequence of improved tumor growth that resulted from posttransfusion immunosuppression (Gantt, 1981). The mechanisms of transfusion-induced immunosuppression are thought to be diverse, including an increase in the number and activity of suppressor T lymphocytes, a reduced lymphocyte responsiveness, a decrease in natural killer-cell activity, a stimulation of anti-idiotype antibody production and an impairment of lymphocyte blastogenesis (George and Morello, 1986; Wu and Little, 1988). Since the report by Burrows and Tartter, in 1982, it has become evident that blood transfusion in colorectal cancer can be associated with higher tumor recurrence rate and shorter survival (Burrows and Tartter, 1982). This effect was corroborated by later studies on patients with colorectal, lung, breast, gastric and renal cancer (Heiss

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et al., 1994; Hyman et al., 1985; Herman and Kolodziejski, 1993; Sugezawa et al., 1989; Edna et al., 1992). However, some studies showed no disadvantage of blood transfusion on survival and/or recurrence in colorectal, lung, breast, gastric, renal and vulva cancer (Nathanson et al., 1985; Moffat et al., 1987; Keller et al., 1988; Moriguchi et al., 1990; Look et al., 1993).

In cervical cancer, Eisenkop et al. reported the adverse effect on outcome of blood transfusion on cervical cancer stage Ib patients who received blood transfusions (Eisenkop et al., 1990). Since that time, relatively few studies have addressed the impact of perioperative blood transfusion on adverse outcome in patients with cervical cancer, and have arrived at difference conclusions (Morris et al., 1995; Monk et al., 1995; Azuma et al., 1997; Wolterbeek et al., 1998; Lentz et al., 1998). Therefore, to address this issue, we evaluated the effects of blood transfusion during radical hysterectomy with lymph node dissection on the disease-free survival of cervical cancer stage Ib in Songklanagarind Hospital.

Materials and Methods

Two hundred ninety five patients with early stage cervical cancer who underwent radical hysterectomy with pelvic lymph node dissection at the Department of Obstetrics and Gynecology, Songklanagarind Hospital, Faculty of Medicine, Prince of Songkla University between January 1987 and August 2002, were reviewed. Patients diagnosed as FIGO stage Ib cervical cancer were eligible for this study. Patients were excluded if they had had prior conization (n = 47), had a history of immunosuppression (n = 0), or their medical records were incomplete (n = 2). The records of the remaining 246 patients (83.39%) were reviewed for age, parity, chief complaints, duration of symptoms, size of lesions, operative time, blood loss, type of blood transfusion, number of transfusions, adjuvant treatment and outcome, and the pathology reports reviewed for histological type, grade, surgical margin, and nodal status.

All patients were surgically treated with a type III radical hysterectomy (Piver et al., 1974) with pelvic lymph node dissection by a number of gynecologic oncologists, including supervised senior residents. In this study, perioperative blood transfusion was defined as transfusion of any blood product within 2 weeks of the primary procedure. Type of blood transfusion in this study was recorded as autologous or allogenic. The decision to transfuse was at the discretion of the surgeon or anesthesiologist. If the autologous transfused patients received additional allogenic blood component, they were

Table 1. Clinicopathological Characteristics of Transfused (autologous or allogenic) and Untransfused Patients

Characteristic	Untransfused (n = 111)	Transfused (autologous) (n = 38)	Transfused (allogenic) (n = 97)	P -value
Age, yr (mean ± SD)	44.0 ± 9.6a	39.9 ± 6.4b	43.4 ± 9.3a	0.051
Para (median, 95% CI)	3ab (1,7)	2.5a (0, 5)	3b (1, 8)	0.013
Chief complaints (n, %)				
Abnormal vaginal discharge	38 (34.2)	14 (36.8)	45 (46.4)	0.189
Abnormal vaginal bleeding	36 (32.4)	11 (29.0)	40 (41.2)	0.272
Postcoital bleeding	39 (35.1)	19 (50.0)	38 (39.2)	0.268
Pelvic pain	16 (14.1)	6 (15.85)	15 (15.5)	0.968
Check up	16 (14.1)	4 (10.5)	7 (7.2)	0.252
Duration of symptoms, yr (median, 95% CI)	3 (1, 24)	4 (0.5, 20)	3 (0.7 , 12)	0.274
Size of lesion, cm (mean ± SD)	2.01 ± 1.09	2.16 ± 1.24	2.13 ± 1.01	0.649
Operative time, min (mean ± SD)	269.5 ± 61.4a	298.9 ± 59.6b	287.9 ± 66.6b	0.021
Blood loss, cc (mean ± SD)	718.6 ± 306.5a	797.4 ± 339.5a	1393.8 ± 835.8b	0.0001
Number of transfusion, unit (median, 95% CI)	0	1 (1, 2)	1 (1, 4)	0.0001
Histology (n, %)				0.332
Squamous cell	76 (68.5)	20 (52.6)	70 (72.2)	
Adenocarcinoma	30 (27.0)	16 (42.1)	22 (22.7)	
Adenosquamous	4 (3.6)	2 (5.3)	5 (5.2)	
Small cell	1 (0.9)	0	0	
Grade (n, %)				0.379
1		78 (70.3)	27 (71.1)	66 (68.0)
2		23 (20.7)	10 (26.3)	18 (18.6)
3		10 (9.0)	1 (2.6)	12 (13.4)
Margin or Parametrium involvement (n, %)	12 (10.8)	3 (7.9)	11 (11.3)	0.812
Node positive (n, %)	3 (2.7)	2 (5.3)	6 (6.2)	0.606
Adjuvant Treatment (n, %)	13 (11.7)	5 (13.2)	15 (15.5)	0.730

Note; Value within rows not having a superscript in common differ significantly at $P < 0.05$.

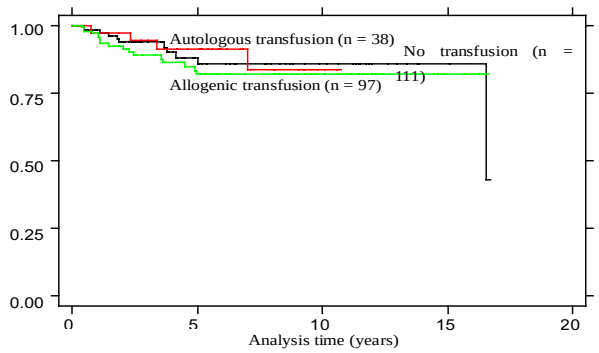

Figure 1. Disease-Free Survival for Cervical Cancer Patients who Received Perioperative Blood Transfusion (autologous or allogenic) and Those not Transfused

classified among the allogenic group.

Further adjuvant radiotherapy depended on the malignant involvement of the lymph nodes or the surgical margin not being free after attempted surgical removal. No concurrent chemoradiation was provided to any patient included in this series.

Most of the patients were scheduled for post-treatment follow up every 1-3 months for 2 years and every 4-6 months until 5 years. After 5 years, the patients were examined once yearly. All living patients who did not show up at the scheduled check up were reminded by phone or mail. All deaths are registered by the Medical Statistical Unit and Cancer Registry Unit of Songklanagarind Hospital and the Department of Provincial Administration, Ministry of Interior, using certificates issued by a physician stating the cause of death.

Disease-free survival (DFS) was calculated from the date that the patients received surgery to the date of appearance a new lesion. DFS profiles of the entire group and subgroups were examined using Kaplan–Meier method. The significance of differences in DFS was evaluated using the log-rank test and significance predictors identified using Cox proportional hazards regression.

Patients and tumor characteristics were compared across the 3 groups using F-test or Kruskal Wallis test as appropriate. A P-value of less than 0.05 was considered to be significant. Stata 7 statistical software (StataCorp, College Station, Tx) was used to perform the analysis.

Results

Of 246 patients with cervical cancer stage Ib evaluated, 111 (45.1%) no received blood transfusion, 38 (15.5%) received autologous blood transfusion and 97 (39.4%) received allogenic blood transfusion. The clinicopathological characteristics of the 246 patients are summarized in Table 1. The mean age at diagnosis for the untransfused, the transfused (autologous) and the transfused (allogenic) groups was 44.0 ± 9.6, 39.9 ± 6.4 and 43.4 ± 9.3 years, respectively. The median parity of all patients in the untransfused and the transfused (allogenic) groups was higher than the transfused (autologous) groups (P = 0.0125). There were no

Table 2. Univariate Analysis of Clinicopathological Prognostic Factors for Disease-Free Survival

Characteristic	5-yr DFS (95% CI)	P-value
Age (yr)		0.163
< 40	84.3 (74.3 , 90.7)	
40-45	95.2 (81.8 , 98.8)	
> 45	81.2 (68.9 , 88.9)	
Para		0.241
< 2	90.5 (67.0 , 97.5)	
2-3	89.1 (81.3 , 93.7)	
> 3	78.5 (65.5 , 87.0)	
Duration of symptoms (yr)		0.393
<2	88.0 (73.5 , 94.8)	
2-4	81.0 (70.6 , 88.1)	
>4	90.4 (79.5 , 95.7)	
Size of lesion (cm)		0.036
<1.5	92.0 (82.9 , 96.4)	
1.5-2.5	84.6 (68.6 , 92.9)	
>2.5	79.2 (67.6 , 87.0)	
Operative time (min)		0.700
<240	82.8 (69.0 , 90.9)	
240-300	86.5 (75.3 , 92.9)	
>300	87.1 (76.5 , 93.1)	
Blood loss (cc)		0.875
<650	85.9 (71.9 , 93.2)	
650-1000	87.2 (77.4 , 93.0)	
>1000	83.8 (71.7 , 91.0)	
Number of transfusion (unit)		0.065
0	88.1 (77.8 , 93.8)	
1	77.5 (64.8 , 86.1)	
>1	92.4 (81.0 , 97.1)	
Histology		< 0.00005
Squamous cell	87.2 (79.7 , 92.0)	
Adenocarcinoma	87.0 (74.3 , 93.6)	
Adenosquamous	68.6 (30.5 , 88.7)	
Small cell	-	
Grade		0.389
1	87.9 (80.9 , 92.5)	
2	78.7 (61.2 , 89.0)	
3	84.7 (59.7 , 94.8)	
Margin or Parametrium involvement		0.528
no	86.6 (80.4 , 90.9)	
yes	79.9 (54.4 , 92.1)	
Node status		0.803
negative	85.5 (79.3 , 90.0)	
positive	90.0 (47.3 , 98.5)	
Adjuvant treatment		0.882
no	86.2 (79.8 , 90.7)	
yes	83.3 (60.8 , 93.5)	
Transfusion status		0.699
Untransfused	88.1 (77.8 , 93.8)	
Transfused (autologous)	90.9 (74.4 , 97.0)	
Transfused (allogenic)	81.7 (71.3 , 88.6)	

significant differences among three groups in chief complaints, duration of symptoms and size of lesion. The most prominent presenting symptoms in our patients were abnormal vaginal discharge, abnormal vaginal bleeding and postcoital bleeding. The mean operative time in transfused blood groups was greater among the untransfused blood group (P = 0.021). However, the mean blood loss in the untransfused group (718.6 cc.) and the transfused (autologous) groups (797.4 cc.) was less than the transfused (allogenic) group (1393.8 cc.) (P = 0.0001).

There was no significant difference in histopathology,

Table 3. Multivariate Analysis of Clinicopathological Prognostic Factors for Disease-Free Survival

Characteristic	HR	95% CI	P-value
Transfusion status			0.613
Untransfused	1		
Transfused (autologous)	1.01	(0.30-3.36)	
Transfused (allogenic)	1.46	(0.64-3.29)	
Age (yr)	1.05	(1.0-1.09)	0.046
Size of lesion (cm)	1.55	(1.06-2.29)	0.024
Histology			0.046
Squamous cell	1		
Adenocarcinoma	1.09	(0.46-2.58)	
Adenosquamous	3.18	(1.05-9.65)	
Small cell	38.10	(3.36-431.8)	

grade, margin or parametrium involvement, node status or postoperative adjuvant treatment among the three groups. The incidence of lymph node positive and margin or parametrium involvement in this study was 4.47% and 10.57%, respectively. The recurrence rate in the transfused (allogenic) groups (15.5%) was higher than the untransfused (9.9%) and the transfused (autologous) groups (10.5%). However, the difference was not significant (P = 0.448).

Five year disease-free survival (DFS) according to potential prognostic variables is shown in Table 2. In univariate analysis, significant differences in 5-year DFS were observed across two factors: histology and size of lesion. The 5-year DFS (and 95% CI) was 90.9% (74.4 - 97.0%) in the transfused (autologous) group, 88.1% (77.8 - 93.8%) in the untransfused group and 81.7% (71.3 - 88.6%) in the transfused (allogenic) group (P = 0.6988).

Discussion

Between 1990 and 2000, few observational studies investigated the effect of blood transfusion on the survival of early stage cervical cancer patients undergoing radical hysterectomy. The roles of perioperative blood transfusion plays in these cases remain controversial. In 2002, gynecologic oncology group (GOG) reported the recurrence free survival and survival in patients with cancer of cervix were not independently related to blood transfusion (Spirtos et al., 2002). This prospective study had included 504 patients who had stage I squamous cell carcinoma. Although it did not have influence for survival, the number of units transfused was found to be significantly related to recurrence-free survival and survival. In the present study, we evaluated the effect of perioperative blood transfusion during radical hysterectomy on prognostic factor retrospectively for disease-free-survival (DFS) in 246 stage Ib cervical cancer patients. There is no evidence that perioperative blood transfusion affects DFS of patients, which is similar to the findings of previous studies (Morris et al., 1995; Monk et al., 1995; Wolterbeek et al., 1998; Lentz et al., 1998). The number of units transfused did not make a difference, which contradicts work by Spirtos (Spirtos et al., 2002). However, some other studies showed correlations between perioperative blood transfusion and adverse outcome (Eisenkop et al., 1990; Azuma et al., 1997). This difference is probably due to the different patient populations, definitions of perioperative blood transfusion, methodology of the patient groups analyzed and prognostic factors other than transfusion-induced immusuppression. In this study, we found only age, size of lesion and histology were statistically significantly associated with DFS.

Current knowledge on the effects of autologous blood transfusion is relatively scarce. Autologous blood transfusion was documented not to lead to any significant immunosuppression in an experimental model (Waymack and Chance, 1988). Data about the survival advantage of autologous blood transfusion in human cancer are available (Kitagawa et al., 2001; Motoyama et al., 2002). Conversely, some randomized controlled trials in surgically treated colorectal cancer patients failed to show significant survival impact of allogenic and autologous blood transfusion (Busch et al., 1993). In our study, the autologous blood transfusion does not impact on DFS after radical hysterectomy. This finding is consistent with the report of Mirhashemi et al (Mirhashemi et al., 1999). However, our results must be cautiously interpreted because of the retrospective nature and limited patient numbers of the study. Although preoperative autologous blood transfusion has been shown to be safe and effective (AuBuchon and Popovsky, 1991; Goodnough et al., 1999), Horowitz et al. reported that autologous blood donation is an expensive medical practice and does not guarantee that exposure to allogenic blood will not occur (Horowitz et al., 2002).

In our opinion, this result failed to support the hypothesis that blood transfusion, be it allogenic or autologous, has a detectable detrimental effect on DFS. Further study or meta-analysis of the impact of perioperative blood transfusion as an independent prognostic factor is required and randomized studies of transfusion alternatives, such as autologous VS allogenous must be of sufficient size to detect small treatment effect. However, perioperative blood transfusion appears to be necessary for anemic patients with the clinical symptoms or signs of inadequate tissue oxygenation.

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