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Intraoperative Transfusion: Is It a Real Prognostic Factor of Periampullary Cancer following Pancreatoduodenectomy?

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Abstract. The purpose of this study was to clarify the prognostic significance of transfusion following pancreatoduodenectomy for periampullary cancers. We analyzed 357 periampullary cancers from 1985 to 1997 (ampullary cancer 130 cases, distal bile duct cancer 141 cases, pancreatic head cancer 86 cases). A total of 215 (60%) of the 357 patients have received intraoperative transfusion. The 5-year survival rate of 130 ampullary cancer patients was 59%; altogether, 76 patients (58%) underwent intraoperative transfusion. The 5-year survival rate of patients without intraoperative transfusion was 79%, whereas that of patients with a transfusion was 47% ($p = 0.029$). Following multivariate analysis, intraoperative transfusion was found to be an independent poor prognostic factor for those with ampullary cancer (relative risk 2.174). Among those with common bile duct cancer, the overall 5-year survival rate was 33%, and the 5-year survival rates for patients with ($n = 87$) or without ($n = 54$) transfusion were 25% and 38%, respectively, which did not reach statistical significance ($p = 0.0717$). For those with pancreatic head cancer, the overall 5-year survival rate was 16%, and there was no survival difference between transfused ($n = 52$) and untransfused ($n = 34$) patients. In the present study the reason was not clear, although intraoperative transfusion was an independent significant prognostic factor for ampullary cancer. Careful dissection to minimize intraoperative bleeding is mandatory during pancreatoduodenectomy for ampullary cancer.

Since the first suggestion that blood transfusion has a negative effect on survival following surgery for colorectal cancer [1], several other cancers including prostate cancer [2, 3], lung cancer [4], cervical cancer [5], osteosarcoma [6], breast cancer [7], and renal cancer [8] have been reported with the same findings. The mechanism for the transfusion's impact is unknown, although suppression of the patient's immune system has been proposed [9].

Pancreatoduodenectomy has been a choice of treatment for periampullary cancer since Whipple popularized it. Initial studies for pancreatoduodenectomy have reported high operative mortality and a poor long-term result. Recently, however, the operative mortality has been reduced to less than 5%, and the 5-year survival rate of those with periampullary cancer exceeds 30% in some specialized institutes [10–12]. Why the prognosis of periampullary cancer after pancreatoduodenectomy has improved is not clear, although a lower incidence of intraoperative transfusion and the use of adjuvant chemoradiotherapy have been suggested to play a role [13, 14].

Few studies have been done about the effect of transfusion on the survival of periampullary cancer patients after resection, and most of the studies that were done were only for pancreatic cancer. The prognostic significance of transfusion in patients with pancreatic cancer was suggested in some reports [15], although the effect was not found in others [16, 17]. Talamini et al. [14] reported that the best predictor of prolonged survival of those with ampullary cancer was the absence of intraoperative transfusion. However, it is still doubtful that transfusion really affects the long-term outcome of periampullary cancer following pancreatoduodenectomy. We presumed that the effect of transfusion on survival might differ in those with pancreatic, bile duct, or ampullary cancer. We have studied a large series of patients following pancreatoduodenectomy for each type of periampullary cancer to clarify the prognostic significance of transfusion in relation to other clinicopathologic factors.

Patients and Methods

We reviewed the medical records of 366 patients who underwent curative pancreatoduodenectomy for periampullary cancer at Seoul National University Hospital between 1985 and 1997 to assess the impact of perioperative blood transfusion on prognosis. Altogether, 9 patients died of postoperative complications, leaving 357 patients for this study. The series included 86 pancreatic head cancers, 141 bile duct cancers, and 130 ampullary cancers. There were 226 men and 131 women with a median age of 59 years (range 22–86 years). A conventional Whipple's operation was performed in 223 patients, pylorus-preserving pancreatoduodenectomy in 119, and total pancreatectomy in 5. The median follow-up interval was 34 months (range 2–154 months), and follow-up was obtained via medical records, letter, or telephone contact and was complete up to September 1999.

The only transfusion product checked in this study was whole blood and packed red blood cells. Analytic variables for possible prognostic factors were the presence of a perioperative transfu-

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sion combined with age, gender, preoperative bilirubin level, weight loss, type of operation, histologic differentiation, tumor size, depth of invasion, and lymph node metastasis.

The cumulative 5-year survival was calculated using the Kaplan-Meier method, and the survival difference across the transfused and untransfused groups was compared using a log-rank test. The analytic variables of the transfused patients were compared with the values for the untransfused patients with a chi-square test. To investigate the combined effects of different variables on survival, Cox's proportional hazards regression model was used. For all tests, a p value of < 0.05 was considered significant. The long-term prognostic significance of perioperative transfusion for overall periampullary cancer, pancreatic head cancer, bile duct cancer, and ampullary cancer were then evaluated.

Results

Intraoperative transfusion was given during 215 (60.2%) of 357 pancreatoduodenectomies. The median and mean amounts transfused were 2.0 and 2.4 units (range 1–14 units), respectively. The cumulative survival of overall periampullary cancer patients is shown in Fig. 1. The actuarial 3-year/5-year survival rates were 46%/39%, and those of untransfused patients were 60%/48% compared with 38%/35% for transfused patients ($p = 0.067$, log-rank test). Because there was a marked difference in the survival rates between patients with pancreatic cancer, bile duct cancer, or ampullary cancer since our previous study (Fig. 2), we examined the prognostic significance of intraoperative transfusion for pancreatic cancer, bile duct cancer, and ampullary cancer, respectively.

Figure 3 shows the survival differences for pancreatic cancer, bile duct cancer, and ampullary cancer according to the transfusion status. A total of 52 patients (60%) with pancreatic cancer received transfusion, and there was no significant difference in survival rates between transfused and untransfused patients ($p = 0.618$). The independent prognostic factors of pancreatic cancer in this study were lymph node metastasis and tumor size (2.5 cm). The survival rate for 87 patients (62%) with bile duct cancer and intraoperative transfusion was lower than for those without transfusion, but the difference did not reach statistical significance ($p = 0.0717$). By multivariate analysis, the only prognostic factor of bile duct cancer was the depth of tumor invasion. Among those with ampullary cancer the 5-year survival rate of 76 (58%) transfused patients was as low as 45% compared with 72% for the untransfused patients; this difference was statistically significant ($p = 0.029$).

Among patients with ampullary cancer, blood transfusion was associated with a poor prognosis when the transfusion was given before or during surgery, not after surgery; transfusion during the entire hospitalization also had an adverse effect on the overall prognosis (Fig. 4). Univariate analysis to determine the prognostic factors for ampullary cancer revealed that the preoperative bilirubin level (5 mg/dl), the presence of percutaneous transhepatic biliary drainage (PTBD), histologic differentiation, the presence of pancreatic invasion, the depth of the tumor, and the presence of lymph node metastasis (as well as preoperative and intraoperative transfusion) were significant (Table 1). By the Cox regression hazard model for the multivariate test using the above possible prognostic variables, depth of tumor, lymph node metastasis, and intraoperative transfusion were significant independent prognostic factors for ampullary cancer. The relative risk of intraoperative transfusion was 2.174 (Table 2).

We compared various clinicopathologic factors according to intraoperative transfusion to determine if there was any difference between transfused and untransfused patients with ampullary cancer. As seen in Table 3, there was no significant difference between the two groups.

Discussion

The mechanisms of the adverse effect of transfusion on the survival and recurrence in cancer patients are not clear. The immunosuppressive effect of transfusion has been proposed as a possible mechanism. Lieberman et al. [18] reported that the transfusion of washed red blood cells induced deficits in cellular immunity and resulted in diminished host survival in a murine neuroblastoma model. The effect was present when allogeneic blood was transfused but was absent with syngeneic transfusion. The deleterious effects of transfusion on tumor recurrence may also be mediated by the increased mitogenic activity observed in stored blood. Increased mitogenic activity was measured in cancer patients following transfusion of stored blood [19].

Clinical evidence of an adverse transfusion effect on the long-term results in cancer patients has been suggested in several reports, particularly for colorectal cancer. However, such effect was not found in other studies. Until now, it seems only a hypothesis that transfused blood suppresses the immune system of the recipient, leading to early tumor recurrence [20].

In this study, transfusion during pancreatoduodenectomy for overall periampullary cancers seemed to induce some difference in the prognosis according to univariate analysis. However, because there are many differences in the biologic characteristics, including long-term prognosis, between pancreatic, bile duct, and ampullary cancers, it is unreasonable to compare the effects of transfusion in overall periampullary cancer patients regardless of the origin of the tumor. Therefore, we attempted to evaluate the significance of transfusion in patients with pancreatic, bile duct, and ampullary cancer, respectively.

In this study, there was no difference in survival between transfused and untransfused patients with pancreatic cancer. In a report from Johns Hopkins Hospital in 1991, intraoperative transfusion was a significant prognostic factor in 81 pancreatic cancer patients between 1969 and 1990 [15]. However, in a follow-up report in 1995, transfusion lost its prognostic significance as the number of patients increased to 201 and the follow-up period was prolonged [13]. In most other reports, intraoperative transfusion was not a prognostic factor for pancreatic cancer [16, 17]. One possibility for the confusing results is that the biology of pancreatic cancer is so aggressive the prognostic difference transfusion may not be evident.

To our knowledge, no previous study has suggested the prognostic significance of transfusion in patients with bile duct cancer. In this study, there was some survival difference between transfused and untransfused patients with bile duct cancer, but the difference did not reach statistical significance. Bile duct cancer is less aggressive than pancreatic head cancer, so the possible effect of transfusion may be shown more concretely with bile duct cancer. With more patients and a longer follow-up period, the adverse effect of transfusion on survival of those with bile duct cancer may have been revealed.

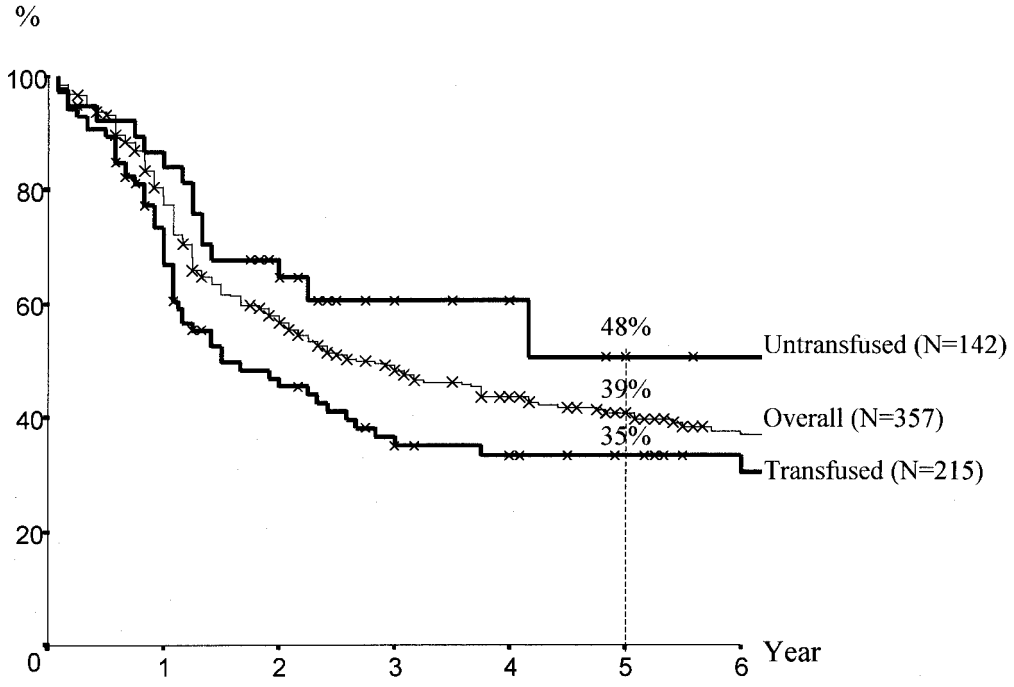

Fig. 1. Cumulative survival curves for 357 periampullary cancers following pancreatoduodenectomy according to intraoperative transfusion. Five-year survival rates of transfused and untransfused patients were 35% and 48%, respectively ($p = 0.067$).

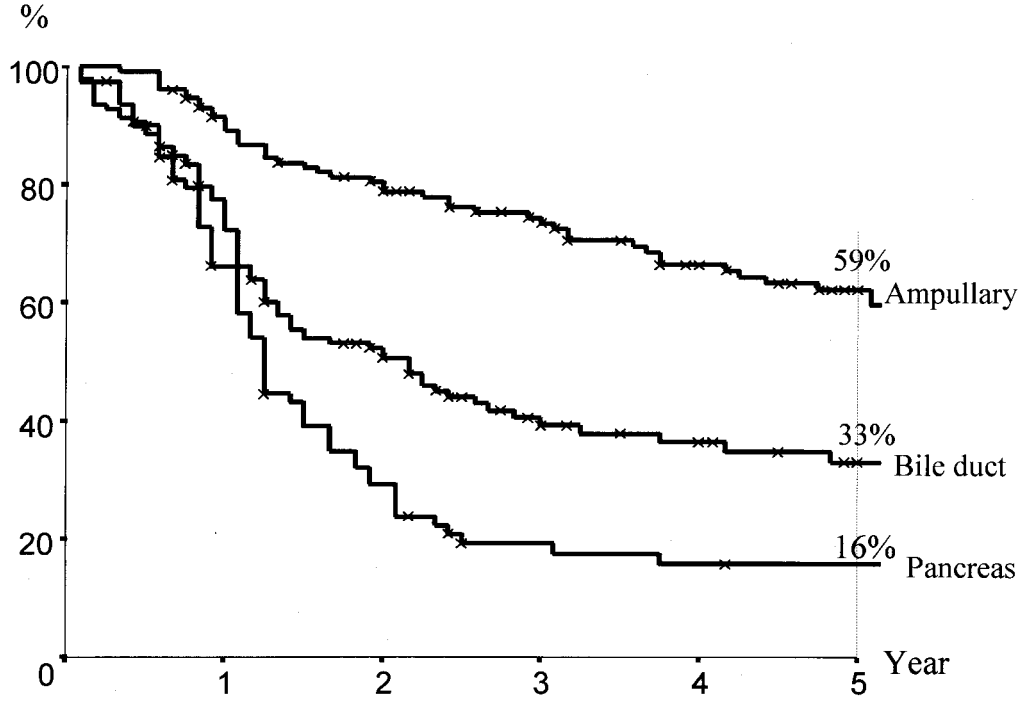

Fig. 2. Cumulative survival curves for patients with pancreatic head cancer, bile duct cancer, or ampullary cancer. There is a marked survival difference between pancreatic, bile duct, and ampullary cancer ($p = 0.000$).

For ampullary cancer, there has been only one study reporting the prognostic significance of intraoperative transfusion. Talamini et al. [14] reported that transfusion was the best predictor of prognosis for patients with ampullary cancer; thus blood transfusion was more important to the prognosis than was tumor biology. Other studies were not in accord with these results [21, 22]. As intraoperative blood transfusion turned out to be a significant prognostic factor by univariate analysis in this study, we attempted to evaluate the effect of transfusion before, during, and after operation, respectively. Though preoperative, intraoperative, and postoperative transfusion all showed negative tendencies for prognosis, preoperative and intraoperative transfusion were shown by univariate analysis to have prognostic significance, whereas postoperative transfusion showed no statistical significance. Because

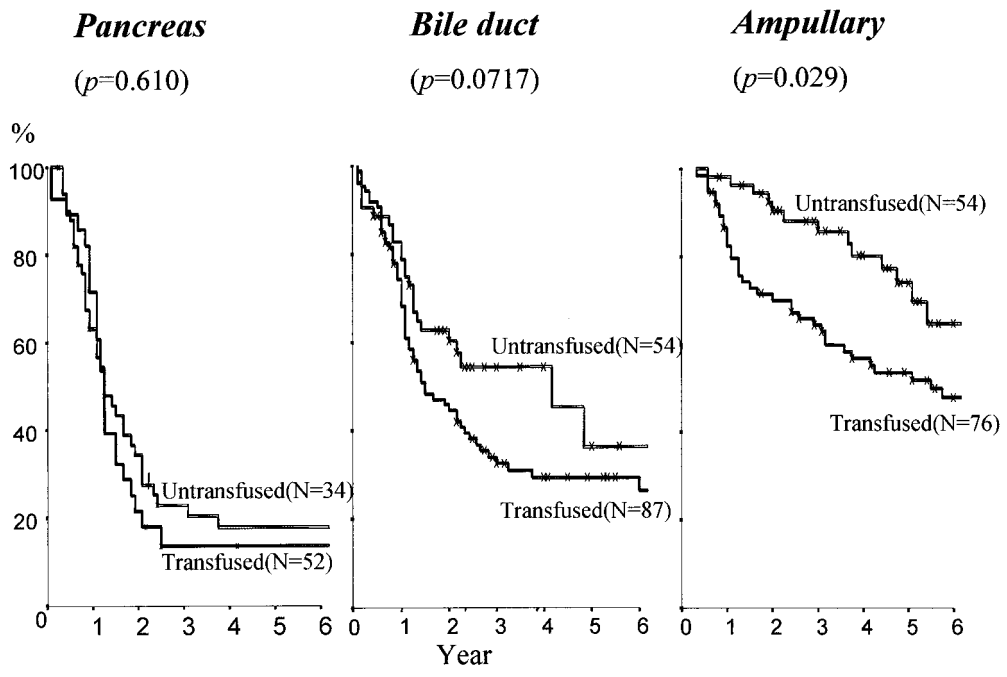

Fig. 3. Cumulative survival curves of pancreatic head cancer, bile duct cancer, and ampullary cancer according to intraoperative transfusion. Intraoperative transfusion had a significant adverse effect only on ampullary cancer patients.

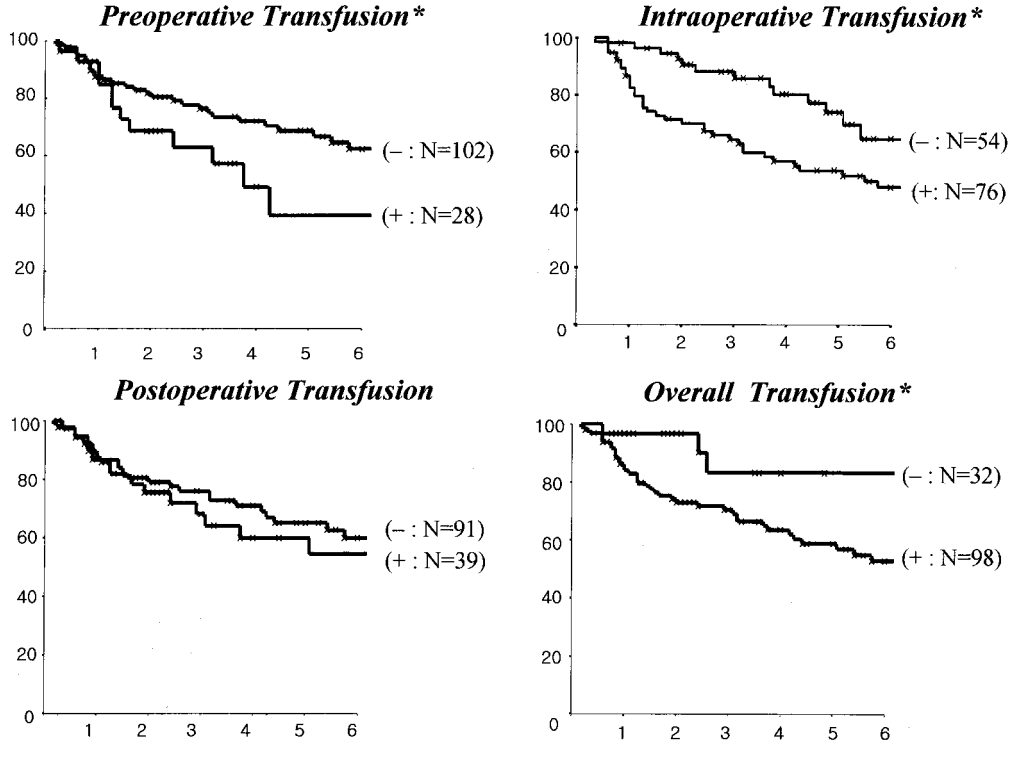

Fig. 4. Survival curves for ampullary cancer patients according to preoperative, intraoperative, and postoperative transfusion. Preoperative, intraoperative, and overall hospital transfusions show significant prognostic significance. *$p < 0.05$.

about half of the postoperative transfusions were given after 5 days postoperatively, the possible immunosuppressive impact of transfusion during the early postoperative period may not be sufficient for changing the patient's outcome. Preoperative transfusion did not have a prognostic significance by multivariate analysis. However, the effect of pre- and postoperative transfusions on the ampullary cancer patient's outcome is not conclusive in this study, and further study is needed. Intraoperative transfusion had an adverse effect on long-term outcome, as shown by multivariate analysis. Because intraoperative immunologic surveillance of cancer patients may be most sensitive and important for early cancer recurrence, intraoperative transfusion could have a significant adverse effect on the prognosis of cancer patients. One previous study evaluated the prognostic significance of perioperative trans-

Table 1. Significant prognostic factors for survival of ampullary cancer patients, by univariate analysis.

Factor	Patients (no.)	5-Year survival rate (%)	*p*
Preop Tf			
No	28	79	0.048
Yes	102	44	
Intraop Tf			
No	57	75	0.029
Yes	73	52	
Total bilirubin			
≤ 5 mg/dl	63	69	0.027
> 5 mg/dl	67	49	
PTBD			
Yes	49	73	0.001
No	81	41	
Histology			
W/D+M/D	73	66	0.044
P/D	57	50	
Pancreas invasion			
No	88	69	0.001
Yes	42	38	
Depth of tumor			
T1	52	75	
T2	34	65	
T3	43	34	
T4	1	0	
Lymph node metastasis			
No	87	72	
Yes	43	36	

Preop Tf: preoperative transfusion; Intraop Tf: intraoperative transfusion; PTBD: percutaneous transhepatic biliary drainage; W/D+M/D: well differentiated and moderately differentiated histology; P/D: poorly differentiated histology.

Table 2. Significant prognostic factors of ampullary cancer, by multivariate analysis.

Factor	Relative risk	95% CI	*p*
Depth of tumor	3.735	1.139–9.158	0.005
Lymph node metastasis	2.335	1.146–6.763	0.028
Intraop Tf	2.174	1.231–3.787	0.039

95% CI: 95% confidence interval.

Table 3. Comparison of the clinicopathologic factors for transfused and untransfused patients with ampullary cancer.

Factor	Transfused	Untransfused	*p*
Age	56.3 ± 9.3	53.0 ± 10.3	0.17
Gender (M:F)	39:36	31:21	0.61
Weight loss	56%	68%	0.19
Total bilirubin (mg/dl)	9.1 ± 6.4	7.3 ± 4.8	0.26
Preoperative PTBD	37%	42%	0.66
Histology (W/D+M/D)	67%	42%	0.14
Pancreas invasion	29%	21%	0.47
T stage (T1+T2)	59%	73%	0.13
Lymph node metastasis	32%	34%	0.82

fusion before, during, and after operation in colorectal cancer patients. In that study preoperative, intraoperative, and postoperative transfusions were all associated with cancer recurrence [20].

It is interesting that in this study intraoperative transfusion was an independent prognostic factor only for ampullary cancer and not for pancreatic or bile duct cancer. A possible reason is that ampullary cancer has the least aggressive biology, so the adverse prognostic impact of transfusion could be seen only for ampullary cancer, as mentioned above.

A dose-dependent relation between transfusion and survival has been reported for colorectal liver metastasis [23] and renal cancer [3]. There also have been reports that the risk of recurrence did not increase progressively with the number of units of blood given [20]. We analyzed the survival difference according to the amount of transfusion but found no dose-related risk of transfusion for ampullary cancer.

The long-term results following pancreatoduodenectomy for periampullary cancer have markedly improved. Recently, the overall 5-year survival rate was reported to be more than 30%, and those for pancreatic, bile duct, and ampullary cancer were better than 20%, 30%, and 50%, respectively [10–12]. The most significant prognostic factor after pancreatoduodenectomy for periampullary cancer is the site of origin of the carcinoma. Other factors have been suggested as well, including lymph node metastasis, depth of invasion, tumor size, and histologic differentiation. The reasons for the improvement in the long-term outcome following pancreatoduodenectomy are not clear, although more extensive dissection, accumulation of experience by hospital specialization, combined adjuvant therapy, and lower incidence of intraoperative transfusion have been proposed as the possible causes [10, 13, 16]. In our hospital, the transfusion rate during pancreatoduodenectomy during the 1980s decreased markedly during the 1990s. For the last 3 years, intraoperative transfusion has been performed in fewer than 20% of cases during pancreatoduodenectomy. The criteria for transfusion we adopted recently is not to transfuse until the hemoglobin level is less than 7 to 8 mg/dl so long as the patient is hemodynamically stable.

Conclusions

Perioperative blood transfusion, particularly intraoperative transfusion, seems to have an adverse effect on survival of patients undergoing pancreatoduodenectomy for ampullary cancer. The prognostic impact of transfusion on patients with pancreatic cancer or bile duct cancer may not be crucial. The practical implication is that transfusion should be given only when essential. In particular, precautions should be taken during the pancreatoduodenectomy to avoid unnecessary hemorrhage. The long-term prognosis could be influenced by the surgeon's ability to avoid intraoperative blood transfusion. Further study of the mechanism and clinical impact of transfusion in periampullary cancer patients is needed.

Résumé. Le but de cette étude a été de déterminer la signification pronostique de la transfusion après duodénopancréatectomie céphalique (DPC) pour cancer périampullaire. Nous avons analysé les dossiers des patients atteints de cancers périampullaires, observés entre 1985 et 1997 (130 cancers ampullaires; 141 cancers des voies biliaires distales et 86 cancers de la tête du pancréas). 215 patients (60%) parmi 357 patients en tout ont reçu une transfusion peropératoire. La survie à 5 ans des 130 patients ayant un cancer ampullaire a été de 59% et 76 patients (58%) ont eu une transfusion peropératoire. La survie à 5 ans des patients sans transfusion peropératoire a été de 79%, alors que celle des patients nécessitant une transfusion a été de 47% ($p = 0.029$). Selon une analyse multivariée, la transfusion peropératoire était un facteur indépendant de

mauvais pronostic dans le cancer ampullaire (risque relatif: 2.174). Dans le cancer de la voie biliaire principale, la survie globale à 5 ans a été de 33% avec des survies à 5 ans des patients avec ($n = 87$) ou sans ($n = 54$) transfusion, respectivement, de 25% et de 38%, différence sans signification statistique ($p = 0.0717$). Dans le cancer de la tête, la survie globale à 5 ans a été de 16%, sans différence significative de survie entre les patients transfusés ($n = 52$) ou pas ($n = 34$). Dans notre étude, bien que la raison ne soit pas claire, la transfusion peropératoire était un facteur pronostique significatif dans le cancer ampullaire. Il faut donc insister sur une dissection soigneuse pour minimiser les pertes sanguines peropératoires dans la DPC céphalique pour cancer de l'ampoule de Vater.

Resumen. El propósito del presente estudio fue determinar el valor pronóstico de la transfusión luego de pancreatoduodenectomía por cáncer periampular. Analizamos 357 pacientes entre 1985 y 1997 (cáncer ampular 130, cáncer de la vía biliar distal 141, cáncer de la cabeza del páncreas 86); 215/357 pacientes (60%) recibieron transfusión intraoperatoria. La tasa de supervivencia a 5 años de los 130 casos de cáncer ampular fue 59% y 76 (58%) recibieron transfusión intraoperatoria. La tasa de supervivencia a 5 años de los pacientes que no recibieron transfusión intraoperatoria fue 79%, en tanto que la de los pacientes que la recibieron fue 47% ($p = 0.029$). En el análisis multivariado la transfusión intraoperatoria aparece como factor insignificante independiente en el cáncer ampular (riesgo relativo 2.174). En el cáncer del colédoco, la tasa global de supervivencia a 5 años fue 33%, y las tasas de supervivencia a 5 años de los pacientes con ($n = 87$) o sin ($n = 54$) transfusión, fueron 25% y 38%, respectivamente, lo cual no alcanza significación estadística ($p = 0.0717$). En el cáncer de la cabeza del páncreas, la tasa global de supervivencia a 5 años fue 16% y no se observaron diferencias de supervivencia entre los pacientes transfundidos ($n = 52$) y los no trasfundidos ($n = 34$). En el presente estudio, aunque la razón no es clara, la transfusión intraoperatoria aparece como un factor pronóstico independiente de significación en cuanto al pronóstico en el cáncer ampular. Se requiere una disección meticulosa para minimizar el sangrado intraoperatorio al practicar una pancreatoduodenectomía por cáncer ampular.

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