Original Paper

Postoperative Host Responses in Elderly Patients after Gastrointestinal Surgery

M Ishikawa[1], M Nishioka[1], N Hanaki[1], T Miyauchi[1], Y Kashiwagi[1], H Miki[1]
Y Kawasaki[2], H Kagawa[2], H Ioki[2], Y Nakamura[2]
[1]Department of Surgery, and [2]Clinical Research Center, National Kochi Hospital, Japan
Corresponding Author: Masashi Ishikawa, MD, PhD, Department of Surgery, Tokushima Red Cross Hospital
1-28 Shinkai, Chuudenn, Komatsujima City, Tokushima, Japan
Tel: +81 8853 2 2555, Fax: +81 8853 2 6350, E-mail: masa1192@tokushima-med.jrc.or.jp

KEY WORDS:
Elderly patients; Th1/2 balance; Energy expenditure; Pulse dye-densitometry

ABBREVIATIONS:
Interferon (IFN); Interleukin (IL); Cardiac Index (CI); Cardiac Output (CO); Blood Volume (BV); Laparoscopic Cholecystectomy (LC); Systemic Inflammatory Response Syndrome (SIRS)

ABSTRACT

Background/Aims: The age-associated dysregulation of hemodynamic, metabolic and immune responses contributes to the high incidence of complications after major abdominal surgery.

Methodology: Ninety-five patients who underwent gastric resection (n=51) and colorectal resection (n=44) were divided according to age into Groups A (n=45, less than 70 years old), B (n=30, 70-79 years) and C (n=20, over 80 years). Flow cytometric analysis of $CD4^+$ lymphocytes for interferon (IFN)-γ and interleukin (IL)-4 production determined the Th1/2 balance. Energy expenditure was measured by indirect calorimetry, and hemodynamics were studied using pulse dye densitometry.

Results: Surgical procedures, operating time, blood loss and morbidity did not significantly differ among the three groups. The cardiac index (CI) in group A and B increased significantly over preoperative levels until POD 3, but there were no significant perioperative changes in the CI levels of group C. Resting energy expenditure levels changed similarly to those of CI. The postoperative Th1/2 ratio decreased from young to elderly to very elderly patients, although no differences were significant before surgery. The postoperative percentage of $CD4^+$IFN-γ+T cells (Th1) in group C decreased significantly despite of no significant changes in that of group A and B. In contrast, the ratio of $CD4^+$IL-4+T cells (Th2) in the all groups significantly increased after surgery.

Conclusions: Host responses in elderly patients after major abdominal surgery were more hyperdynamic and hypermetabolic than those of young patients. Postoperative dysregulation of the Th1/2 balance was also associated with aging. However, host responses appear to significantly differ between elderly and very elderly patients.

INTRODUCTION

Chronological age is a predictor of a decreased postoperative survival rate. Aging causes disease, and the aging process adversely affects the survival of the organism and recovery from disease. Host responses to surgical stress and infection are altered with aging, and increased susceptibility to postoperative complications is age-related. Classical studies have demonstrated that aging results in decreased energy metabolism and hemodynamics such as cardiac output and circulating blood volume (1). Cardiac output trends downward with aging for various reasons. Early diastolic filling in individuals at age 70 is only one half of that of individuals at age 30. Diastolic dysfunction is the primary cause of heart failure in the elderly, but systolic function is normal or nearly normal in most of such patients. However, perioperative changes in cardiac output and circulating blood volume between young and elderly patients have rarely been compared. Hemodynamic changes can now be assessed at the bedside using dye densitometry as accurately as using the Swan Ganz method (2,3).

Surgical trauma induces metabolic alterations, including changes in energy metabolism. Several evaluations of energy changes have demonstrated that surgical procedures generally cause only a small increase (up to 30%) in resting energy expenditure, and efforts have been made to control for confounding factors that may influence energy metabolism (4,5). However, little is known about how perioperative energy metabolism changes in elderly patients.

Immunosenescence is associated with a deterioration of both cellular and humoral immunity (6,7). Although these changes are subtle, they ultimately result in altered responses to stress and infection. Mosmann *et al.* (8) classified murine $CD4^+$ helper T cells as Th1 and Th2, according to cytokine profile. Other studies have shown that the secretion of Th1-cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2) is decreased in the elderly after lymphocyte stimulation (9,10). However, a few investigators have published controversial results regarding Th2-cytokines in the elderly (11,12). Further studies are required to clarify the interaction of the Th1/2 balance before and after surgery in the elderly. Many aspects of immune function, including the Th1/2 balance, would be dysregulated in the elderly, and cytokines are important in the development of pathological states. Therefore, we surmised that age-associated changes in the immune system will affect the host

Hepato-Gastroenterology 2006; 53:730-735

response after surgical procedures, including metabolic and hemodynamic changes. Here, we compared the perioperative immune, metabolic and hemodynamic responses of elderly and young patients who underwent abdominal surgery.

METHODOLOGY

Ninety-five patients (48 males, 47 females; mean age, 67±11 years) underwent abdominal surgery at our clinic between April 1999 and April 2002. The Research Committee of National Kochi Hospital approved the experimental protocol. All patients understood the nature and risk of this study, and written informed consent was obtained from all of them to participate. Fifty-one gastric resections for gastric cancer and 44 colorectal resections for colorectal cancer were performed. The patients were divided according to age into groups A (n=45), young patients (less than 70 years old), B (n=30), elderly patients (70-79 years old) and C (n=20), very elderly patients (over 80 years old). **Table 1** shows the characteristics of each group. The distribution of surgical procedures did not significantly differ among the groups. Six (13%) patients in group A, 7 (23%) in group B and 6 (30%) in group C had preoperative complications such as hypertension, angina, diabetes mellitus and cerebral infarction. Electrocardiograms and echograms did not reveal obvious changes in any of the patients. The procedures for groups A, B and C lasted 246±65, 178±166 and 251±283 min, respectively, with operative blood losses of 324±323, 278±331mL and 232±117mL, respectively. These data were not significantly different among the groups. None of the patients received steroids, low-dose dopamine or selective gut decontamination. Antibiotics were administered according to a predetermined protocol that was modified if specific microbiologic information became available. None received enteral nutrition and intravenous hyperalimentation during the study and patients who developed postoperative complications such as leakage, abdominal abscess and pneumonia, were excluded in the study. Thirty-seven patients [16 (36%) in group A, 13 (434%) in group B and 8 (40%) in group C] postoperatively developed systemic inflammatory response syndrome (SIRS) (13).

All patients were studied in the morning while resting in bed and before other examinations. Patients who were ventilated mechanically were excluded from the study.

Flow Cytometric Determination of Intracellular IFN-γ and IL-4 Expression

Blood was sampled before surgery, on POD 2 and 14. The proportion of CD4 positive lymphocytes producing IFN-γ and IL-4 were measured by flow cytometry as described by Openshaw *et al.* (14). Briefly, 1mL of blood was immediately mixed with 10μg/mL of Brefeldin A (Sigma B7651) at ambient temperature, within 2 hours of withdrawal. Peripheral blood lymphocytes were harvested, washed, and resuspended at a density of 10^5-10^6/mL and stimulated with PMA 50ng/mL (Sigma P8139) plus ionomycin (Sigma 10634) 500ng/mL. After a wash and a 10-min incubation in PBS containing BSA and saponin, lymphocytes were incubated with anti-CD4 monoclonal Ab and anti-IFN-γ DAKO, RG285) or anti-IL-4 (DAKO, RG204) for 30 min before adding an equal volume of 4% formaldehyde fixative. Samples were analyzed using a FACScan flow cytometer (Beckman Coulter). Results were analyzed using the XL/XL-MCL system and calculated as a ratio (%) of IFN-γ-producing (Th1) to IL-4-producing (Th2) cells.

Resting Energy Expenditure Measurements

We measured resting energy expenditure (REE) and the respiratory quotient (RQ) by indirect calorimetry using a ventilated hood system (Vmax29, SensorMedics, California, USA) preoperatively and on postoperative days 1, 3, 7, and 14. The REE value was calculated from the measured volume of oxygen utilization and carbon dioxide output, as described (15). Dry gases were measured and the results were converted to a standard temperature and pressure. Flow through the canopy was kept constant at a rate that was adjusted according to the body weight of the patient (28-36L/min). The predicted REE for each patient was calculated on the day of examination using the Harris-Benedict Equations (16).

Cardiovascular Studies

Cardiac output (CO), Cardiac index (CI), Blood volume (BV) and K-ICG were measured preoperatively and on POD 1 and 3 using a DDG-2001 apparatus (Nihon Koden, Tokyo, Japan) as described (17). Briefly, the probe was secured on one nostril or finger, and after sampling blood to measure hemoglobin, 20mg ICG was injected via an antecubital venous line while the DDG was recorded for 10 min. Pulse dye-densitometry is based on the principle of pulse spectrophotometry. The ratio of the blood ICG to the hemoglobin concentration was measured at wavelengths of 805 and 890nm. Because the extinction coefficient of ICG in blood is maximal at 805nm and almost zero at 890nm, and since the difference in the oxyhemoglobin and reduced hemoglobin extinction coefficients at these wavelengths is negligible, the ICG concentration can be calculated from the ratio of its concentration to the total hemoglobin concentration for each pulse. In addition, the elimination rate constant (K) of ICG (K-ICG), which is equivalent to

TABLE 1 Characteristics of Each Group

	Case	M:F	Disease	Operating Duration (min)	Blood loss (mL)
Young pts	45	23:23	gastric ca 27		
(less than 69yrs)			colon ca 18	246±65	324±323
Elderly pts	30	15:15	gastric ca 16		
(70-79yrs)			colon ca 14	178±166	279±332
Very elderly pts	20	11:9	gastric ca 8		
(over 80yrs)			colon ca 12	251±283	232±117

hepatic blood flow, was calculated from an ICG elimination curve detected by the DDG analyzer.

Statistical Analysis

Values for results are presented as means±SD. Continuous variables were compared using Student's *t* test. Differences between the two groups with respect to variable times were compared using the analysis of variance (ANOVA) for repeated measures. A *p* value of <0.05 was considered significant.

RESULTS

Changes in Hemodynamics

The cardiac index (CI) values of the young, elderly and very elderly patients were similar before surgery. The preoperative means±SD of CI were 2.81±0.60, 2.63±0.96 and 2.47±0.73L/min/m^2 for young, elderly and very elderly patients, respectively **(Figure 1)**. The CI in the young and elderly patient groups increased significantly over preoperative levels until POD 3. However, the perioperative CI levels did not significantly change in the very elderly patients. Significant differences in the preoperative values of BV were found among the three groups (A, 4.4±0.7; B, 3.7±0.9 and C, 2.9±0.8L; *P*<0.05). Postoperative BV values significant decreased in the order of young, elderly and very elderly patients (A, 4.0±0.9; B, 3.5±0.8 and C, 2.6±0.8L on POD 1; *P*<0.05). Postoperative BV values in each group did not significantly change. The preoperative K-1CG level of the young patients was significantly higher than those of the elderly and very elderly patients (A, 0.22±0.04; B, 0.18±0.05 and C, 0.17±0.04; *P*<0.05). The K-ICG levels in all groups significantly increased until POD 3 then they gradually decreased until POD 14.

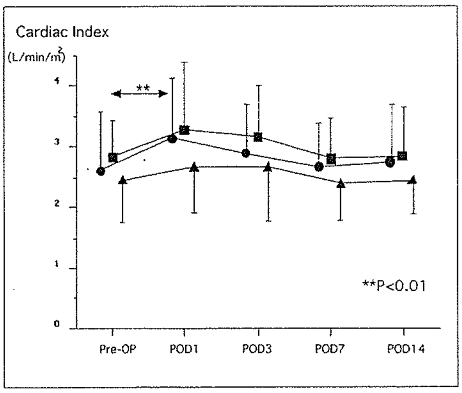

FIGURE 1 Changes in cardiac index (CI) (■-■ young, ●-● elderly, ▲-▲; very elderly patients). CI in young and elderly patients significantly increased over preoperative levels until POD 3. However, perioperative CI levels did not significantly change in the very elderly patients.

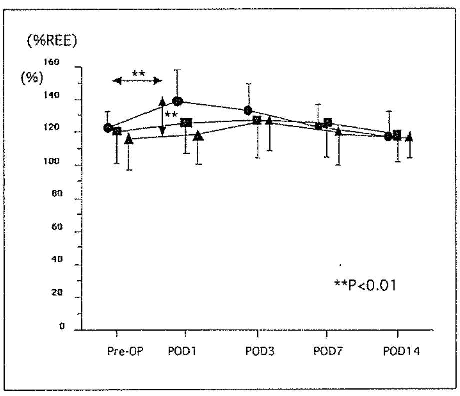

FIGURE 2 Changes in %REE (■-■ young, ●-● elderly, ▲-▲; very elderly patients). The REE levels in the elderly groups significantly increased until POD 3 compared with the preoperative level but postoperative levels in the other two groups did not significantly increase. On POD 1, the REE in the elderly groups was significant high compared with that in young and very elderly groups (*P*<0.01).

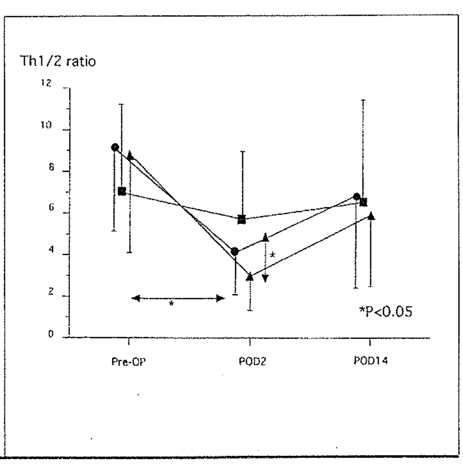

FIGURE 3 Changes in Th1/2 ratio according to age (■-■ young, ●-● elderly, ▲-▲; very elderly patients). Preoperative ratios of Th1 to Th2 among the three groups did not significantly differ, but the postoperative ratio of Th1 to Th2 decreased significantly in all patients from 8.2±4.to 4.5±3.0 on POD 2. The ratio of Th1 to Th2 in the super-elderly patients group obviously decreased to 3.0±1.7 on POD 2, which was significantly different (*p*<0.05) from those in young (5.7±4.2) and in elderly (4.1±2.0) patients. The Th1/2 ratio in all groups recovered to preoperative levels by POD 14.

Changes in Energy Metabolism Measured by Indirect Calorimetry

The mean amounts of weight lost by the patients by POD 7 was significantly (*p*<0.05) higher in group A [3.6±1.5 (6.6%)] and B [3.5±1.3 (6.8%)] compared with that of group C [2.6±1.5Kg (5.2%)]. Preoperative REE levels did not significantly differ among the three groups. The REE levels in the elderly groups significantly increased until POD 3 compared with the preoperative level but the postoperative levels of the other two groups did not significantly increase **(Figure 2)**. On POD 1, the REE in the elderly groups was significantly higher that that in the young and very elderly groups (A, 124±18%; B, 139±18%; C, 117±18%; *P*<0.05). The preoperative RQ level also did not significantly differ among the three groups. The RQ significantly decreased to around 0.8 immediately after surgery and returned to near preoperative levels on POD 14 in all groups.

Balance of Th1/2 Analyzed by Flow Cytometry

The lymphocyte counts in all groups were similar before surgery and decreased significantly after surgery, reaching a nadir of almost one-third of the baseline on POD 2. However, lymphocyte counts before and after surgery among the three groups did not significantly differ. The preoperative ratios of Th1 to Th2 among the three groups also did not significantly differ, the means being 7.1±5.1, 9.0±5.0 and 8.8±6.6 in the young, elderly and very elderly patients, respectively **(Figure 3)**. The postoperative ratio of Th1 to Th2 decreased significantly in all patients to 4.4±3.0 on POD 2 from 8.3±4.2. The ratio of Th1 to Th2 in the very elderly patients obviously decreased to 3.0±1.6 on POD 2, and was significantly different (*p*<0.05) from those in the young (5.7±4.1) and elderly (4.1±2.1) patients. The Th1/2 ratios in all groups recovered to preoperative levels by POD 14.

The ratios (%) of CD4+IFN-γ+T cells among the three groups did not significantly differ before surgery (14.7±9.6%, 12.7±6.1% and 16.2±4.7% in young, elderly and super-elderly patients, respectively; **Figure 4a**). Although the percentage of $CD4^{+}IFN\text{-}\gamma$ +T cells did not significantly change in the young and elderly patients postoperatively, that of the very elderly decreased significantly to 10.4±6.3% on POD 2, and remained at a low level by POD 14. In contrast to $CD4^{+}IFN\gamma$- +T cells, the ratio (%) of CD4+IL-4+T cells in all patients significantly increased to 4.8±3.5% on POD 2 from a preoperative value of 3.3±4.2% (**Figure 4b**).

DISCUSSION

In elderly patients, the postoperative mortality rate increased with each decade beyond the age of 70 (18). Boyed *et al.* Showed a mortality rate of 5% in patients aged 70-79, and 17% in patients over 80 (19). Therefore, we selected patients older than 70 years and 80 years to evaluate the differences in host responses after gastrointestinal surgeries. Our data showed that the cardiac index and REE obviously increased at the early postoperative stage among elderly patients although the background did not significantly differ except for age between the young and very elderly patients. The cardiac index and REE did not significantly increase in the very elderly patients. Surgical stress causes an increase in cardiac output among both young and old patients but by very different mechanisms (20). Both the heart rate and stroke volume are increased in young patients by increasing the efficiency of contraction and by decreased end systolic volumes. However, the heart rate changes little in older patients; instead, stroke volume is increased. Although coronary artery disease increases considerably with advanced age, much of it does not become evident until after the stress of surgery.

Over the last 20 years, two major studies have focused on predicting cardiac risk for elderly patients undergoing noncardiac surgery. Goldman *et al.* (21) studied 1001 patients undergoing noncardiac surgery and established criteria that predict significant postoperative cardiac complications. Although age of over 70 years is a risk factor in the Goldman criteria, it does not carry statistical weight according to discriminant analysis as an active cardiac disease. Gerson *et al.* (22) showed that the most predictive test for postoperative cardiac and pulmonary complications among 100 patients above 65 years of age was exercise tolerance. Patients who could not exercise on a bicycle for 2 minutes and whose heart rate could not be increased beyond 100 beats per min were at a six-fold and five-fold increased risk for cardiac and pulmonary complications respectively. However, little is understood about perioperative hemodynamics among elderly patients undergoing major abdominal surgery. The integrated pulse spectrophotometry system used in the present study is less invasive and can be repeatedly applied within a short period without blood sampling (23). This method is useful for estimating the cardiac output, circulating blood volume and liver blood flow of gastrointestinal patients with a single bolus injection of ICG. No routine bedside monitoring has been used to estimate blood volume other than the Swan Ganz catheter. To our knowledge, the present study is one of the first perioperative comparisons of hemodynamics including cardiac index and blood volume between young and aged patients.

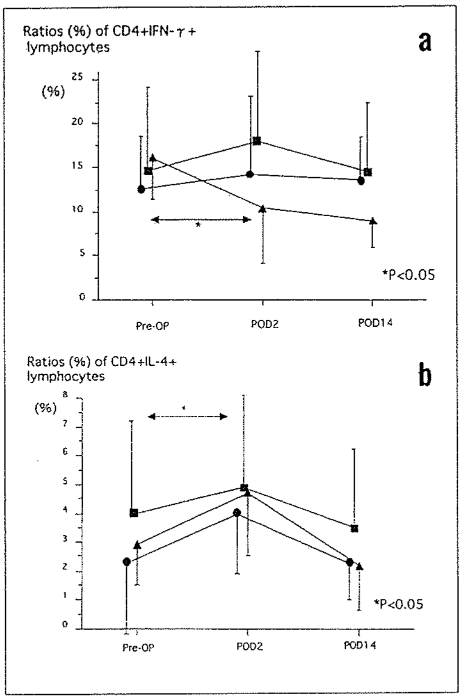

FIGURE 4 Preoperative and postoperative lymphocyte ratios (A, B and C, young, elderly and very elderly patients, respectively) **a)** and **b)**, Ratios (%) of $CD4^{+}IFN\text{-}\gamma$ + and $CD4^{+}IL\text{-}4$+ lymphocytes, respectively. The postoperative ratio of $CD4^{+}IFN\text{-}\gamma$ +T cells (Th1) in group C significantly decreased whereas those in groups A and B did not. In contrast, the postoperative ratio of $CD4^{+}IL\text{-}4$+T cells (Th2) significantly increased in all groups.

The amount of the early postoperative increase in REE was significantly in elderly patients compared with young and very elderly patients. Many studies have evaluated the energy expenditure associated with elective surgery (4,24). These studies have focused on not aging but surgical procedures. Surgical stress is characterized by hypermetabolism, accelerated tissue breakdown and loss of protein, resulting in weight loss and postoperative fatigue. Weight loss after abdominal surgery is usually due to a combination of increased energy expenditure secondary to the endocrine-metabolic response to injury, a decrease in dietary intake and increased metabolic requirements imposed by cancer. This study found that the mean weight loss of young and elderly patients during the period before surgery and POD 7 was significantly higher than that of very elderly patients. In general, the Harris and Benedict (HB) formula to predict REE in the elderly population may be questionable. Owen *et al.* (25) showed that REE is slightly underestimated by the HB formula in patients over 64 years of age. Fredrix *et al.* (4) showed that the HB formula underestimates REE by approximately 7% in healthy volunteers over 50 years of age. Therefore, the present study would have overestimated the %REE as a percentage of the reference value, and intragroup postoperative and preoperative %REE values were usually compared. Douglas and Shaw (26) found numerous factors to account for the increase in energy metabolism after surgical trauma. In addition to stress responses, energy metabolism is influenced by substrate metabolism, type and amount of calories, and other physiological differences such as increased body temperature. Most factors in the present study, such as calorie intake and the ratio of patients with fever did not significantly differ among the three groups. Therefore, we suspected that stress-induced mediators, such as IL-1, IL-6 and tumor necrosis factor, prostanoids, hormonal mediators, oxygen free radicals and their products caused the increase in energy metabolism. Indeed, Fagiolo *et al.* (27) reported significantly increased levels of IL-6, TNF-α and IL-1β in mitogen-stimulated cultures from aged donors. Although changes in postoperative RQ did not significantly differ according to age, the increase in REE was associated with a RQ in the 0.8 range, which was much higher than that of starvation (0.7) and much lower than that of glucose oxidation in the present study. This indicates that mixed fuel oxidation, namely with glucose, amino acids and fat did not significantly differ with age.

Although we did not measure circulating cytokine levels in our patients, we suspected that hemodynamics and energy expenditure were most prominent in the elderly patients due to age-related perturbation of mediators of the immune system. However, we also supposed that elderly individuals over 80 years old are less able to regulate hemodynamics and metabolism under stress although their systems function perfectly well at rest. The present study showed that the postoperative Th1/2 ratio decreased in the order of young to elderly to very elderly patients. Among the latter, the decrease in the number of $CD4^+IFN\text{-}\gamma^+$ T cells was accompanied by a simultaneous postoperative increase in that of $CD4^+IL\text{-}4^+$ T cells although the number of $CD4^+IFN\text{-}\gamma^+$ T cells in the young and elderly patients did not significantly change. The results of the present study are consistent with those of previous reports demonstrating that major surgery suppresses the potential responses of Th1 cytokines and significantly decreases IFN-γ and IL-2 production by mononuclear cell cultures from elderly individuals (28,29). In general, the delayed type hypersensitivity response, lymphocyte proliferation and cytotoxic T lymphocyte activities decrease with aging while the numbers of memory T cells and the antibody response increases (30). However, reports of age-related changes in the production of proinflammatory cytokines are inconsistent. Caruso *et al.* (11) showed that IFN-γ and IL-2 production of mononuclear cells from elderly individuals significantly decreased but IL-4 and IL-6 production did not significantly differ between cultures from elderly and from young patients. Cakman *et al.* (9) also showed decreased production of IFN-γ and soluble IL-2 receptor in the elderly, whereas that of IL-10 was greater than in young controls. These findings suggest that a dysregulated Th1/2 balance causes the type of immune response observed in the elderly individuals. However, perioperative changes in the Th1/2 balance of elderly patients have not been studied. We recently demonstrated that the preoperative Th1/2 ratio of patients with a malignancy was significantly lower that that of patients with laparoscopic cholecystectomy (LC), and that the Th1/2 ratios on POD 2 of patients who underwent gastric and colorectal resection were significantly decreased compared with those who underwent LC (31). Decker *et al.* (32) also reported that the Th1/2 balance was quite different between LC and open cholecystectomy patients, showing that down-regulation of the Th1 immune response or cell-mediated immunity increases patient susceptibility to infection by viruses or intracellular bacteria. The age-related changes in the Th1/2 balance may be directly or indirectly associated with impaired protective immunity, by affecting the ability to deal with infections or tumors. The reduced amounts of IFN-γ on $CD4^+$T cells shown in the present study, might significantly contribute to the increased susceptibility of elderly individuals to infections and tumors.

In conclusion, the host responses of elderly patients after major abdominal surgery were more hyperdynamic and hypermetabolic than those in young patients. In contrast, the postoperative host responses of very elderly patients were mild. Cytokines, including the Th1/2 balance became dysregulated with aging. These findings suggest that host responses significantly differ between elderly and very elderly patients. Therefore, the postoperative management of aged patients should consider the metabolic, hemodynamic and immunological changes associated with aging.

REFERENCES

1 **Kohn RR:** Human aging and diseases. J Chron Dis 1963; 16:5-12.

2 **Iijma T, Aoyagi T, Iwao Y, Masuda J, Fuse M, Kobayashi N, Sankawa H:** Cardiac output and circulating blood volume analysis by pulse dye-densitometry. J Clin Monitor 1997; 13:81-89.

3 **Imai T, Mitaka C, Nosaka T, Koike A, Ohki S, Isa Y, Kunimoto F:** Accuracy and repeatability of blood volume measurement by pulse dye densitometry compared to the conventional method using 51Cr-labeled red cell blood cells. Int Care Med 2000; 26:1343-1349.

4 **Fredrix EWHM, Soeters PB, Meyenfeldt MF, Saris WHM:** Resting energy expenditure in cancer patients before and after gastrointestinal surgery. J Parent Ent Nutr 1991; 15:604-607.

5 **Moriyama S, Okamoto K, Tabira Y, Kikuta K, Kurita I, Hamaguchi M, Kitamura N:** Evaluation of oxygen consumption and resting energy expenditure in critically ill patients with systemic inflammatory response syndrome. Crit Care Med 1999; 27:2133-2136.

6 **Ogata K, Tamura H, Yokose N, Dan K, Nomura T:** CD4 lymphopenia and risk of infection in immunogerontologically healthy elderly people. Lancet 1996; 347:1408.

7 **Sansoni P, Cossarizza A, Brianti V, Fagnoni F, Snelli G, Monti D:** Lymphocyte subsets and natural killer cell activity in healthy old people and centenarians. Blood 1993; 82:2767-2773.

8 **Mosmann TR, Coffman RL:** Th 1 and Th 2 cells: Different patterns of lymphokine secretion lead to different functional properties. Ann Rev Immunol 1989; 7:145-173.

9 **Cakman I, Rohwer J, Schutz RM, Kirchner H, Rink L:** Dysregulation between TH1 and TH2 T cell subpopulations

in the elderly. Mech Ageing Dev 1996; 87:197-209.
10 **Berguer R, Bravo CN, Bowyer M, Egan C, Knolmayer T, Ferrick D:** Major surgery suppresses maximal production of helper T-cell type 1 cytokines without potentiating the release of helper T-cell type 2 cytokines. Arch Surg 1999; 134:540-544.
11 **Caruso C, Candore G, Cigna D, DiLorenzo G, Sireci G, Dieli F, Salerno A:** Cytokine production pathway in the elderly. Immunol Res 1996; 15:84-90.
12 **Han SN, Meydani SN:** Antioxidants, cytokines, and influenza infection in added mice and elderly humans. J Infect Dis 2000; 182:S74-80.
13 **Members of the American college of chest physicians/society of critical care medicine consensus conference committee:** American college of chest physicians/society of critical care medicine consensus conference committee: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864-874.
14 **Openshaw BP, Murphy EE, Hosken NA, Maino V, Davis K, Murphy K, O'Garra A:** Heterogenecity of intracellular cytokine synthesis at the single-cell level in polarized T helper 1 and T helper 2 populations. J Exp Med 1995; 182:1357-1367.
15 **Monk DN, Plank LD, Franch-Arcas G, Finn PJ, Streat SJ, Hill GL:** Sequential changes in the metabolic response in critically injured patients during the first 25 days after blunt trauma. Ann Surg 1996; 223:395-405.
16 **Harris JA, Benedict FG:** A biometric study of basal metabolism in man. Carnegie Institute of Washington DC, Publication 1919; 279:233-250.
17 **He YL, Tanigami H, Ueyama H, Mashimo T, Yoshiya I:** Measurement of blood volume using indocyanine green measured with pulse-spectrophotometry: Its reproducibility and reliability. Crit Care Med 1998; 26:1446-1451.
18 **Houry S, Amenabar J, Rezvani A, Huguier M:** Should patients over 80 years old be operated on for colorectal or gastric cancer? Hepatogastroenterology 1994; 41:521-525.
19 **Boyd JB, Bradfoed B, Watne AL:** Operative risk factors of colon resection in the elderly. Ann Surg 1990; 192:743-746.
20 **Zenilman ME:** Surgery in the elderly. Curr Probl Surg 1998; 35:107-178.
21 **Goldman L, Caldera DL, Nussbaum SR, Southwick FS, Krogstad D, Murray B, Burke DS, O'Malley TA, Goroll AH, Caplan CH, Nolan J, Carabello B, Slater EE:** Multifactorial index of cardiac risk in noncardiac surgical procedures. N Engl J Med 1977; 297:845-850.
22 **Gerson MC, Hurst JM, Hertzberg VS, Doogan PA, Cochran MB, Lim SP, McCall N, Adolph RJ:** Cardiac prognosis in noncardiac geriatric surgery. Ann Intern Med 1985; 103:832-837.
23 **Hirasawa K, Kasuya H, Hori T:** Change in circulating blood volume following craniotomy. J Neurosurg 2000; 93:581-585.
24 **Plank LD, Connolly AB, Hill GL:** Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. Ann Surg 1998; 228:146-158.
25 **Owen OE, Holup JL, D'Alessio DA, Polansky M, Smalley KJ, Kavle EC, Bushman MC, Owen LR, Mozzoli MA:** A reappraisal of caloric requirements of men. Am J Clin Nutr 1986; 44:1-19.
26 **Douglas RG, Shaw JHF:** Metabolic rèsponse to sepsis and trauma. Br J Surg 1989; 76:115-122.
27 **Faiolo U, Cossarizza A, Sala E, Fanales-Belasio E, Ortolani C, Cozzi E, Monti D, Franceschi C, Paganelli R:** Increased cytokine production in mononuclear cells of healthy elderly people. Eur J Immunol 1993; 23:2375-2378.
28 **Ono S, Aosasa S, Tsujimoto H, Ueno C, Mochizuki H:** Increased monocyte activation in elderly patients after surgical stress. Eur Surg Res 2001; 33:33-38.
29 **Serra J, Fernandez-Gutierrez B, Hernandez- Garcia C, Vidan M, Banares A, Ribera J, Jover JA:** Early T cell activation in elderly humans. Age and Ageing 1996; 25:470-478.
30 **Peterson PK:** Aging, immunity, and cardiopulmonary bypass surgery: Adding insult to injury. J Lab Clin Med, 1997; 129:578-579.
31 **Ishikawa M, Nishioka M, Hanaki N, Miyauchi T, Kashiwagi Y, Miki H:** Hepatic resection leads to predominance of the T helper-2 lymphocyte phenotype. Hepatol Res 2004; 30:96-103.
32 **Decker D, Schondorf M, Bidlingmarier F, Hirner A, von Ruecker AA:** Surgical stress induces a shift in the type-1/type-2 T-helper cell balance, suggesting down-regulation of cell-mediated immunity commensurate to the trauma. Surgery 1996; 119:316-325.

Original Paper

Results of 404 Hepatic Resections Including 80 Repeat Hepatectomies for Hepatocellular Carcinoma

Akira Kobayashi MD[1], Seiji Kawasaki MD[2], Shin-ichi Miyagawa MD[1], Shiro Miwa MD[1]
Terumasa Noike MD[1], Satoshi Takagi MD[1], Satoru Iijima MD[1], Yusuke Miyagawa MD[1]
[1]First Department of Surgery, Shinshu University School of Medicine, Matsumoto
and [2]Second Department of Surgery, Juntendo University School of Medicine, Tokyo, Japan
Corresponding Author: Seiji Kawasaki MD, Second Department of Surgery
Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, Japan
Tel: +81 3 5802 0434, Fax: +81 3 5802 0434, E-mail: kawasaki@med.juntendo.ac.jp

KEY WORDS:
Liver resection; Hepatocellular carcinoma; Repeat hepatectomy

ABBREVIATIONS:
Hepatocellular Carcinoma (HCC); Indocyanine Green Retention Rate at 15 minutes (ICG-R); Blood Transfusion (BTF); Ultrasonography (US); α-Fetoprotein (AFP); des-gamma-Carboxy Prothrombin (DCP); Computed Tomography (CT); Hepatitis B Antigen (HBsAg); Hepatitis C Antibody (HCVAb)

ABSTRACT

Background/Aims: To evaluate our treatment protocol applied to patients with hepatocellular carcinoma. The protocol consists of the selection criteria for hepatectomy, the use of techniques that minimize intraoperative blood loss, strict follow-up after surgery, and an aggressive surgical approach for intrahepatic recurrence.

Methodology: We conducted a retrospective cohort study that included 337 patients with hepatocellular carcinoma treated between 1990 and 2001. The type of resection was selected according to the serum bilirubin value and the indocyanine green retention rate at 15 minutes. Perioperative data and long-term outcome were examined.

Results: We performed 324 initial hepatectomies with an in-hospital mortality rate close to zero. There was one operative death and one hospital death (0.3% each), and the 5-year survival rate for all patients was 53.2%. Eighty repeat liver resections, including 18 third and two fourth, were performed with no mortality, and the 5-year survival rate was 52.9% after the second hepatic resection. The resectability rate for second and third hepatectomies reached 29% and 33% of all patients with isolated liver recurrence, respectively.

Conclusions: Liver resection is a safe and effective treatment modality for hepatocellular carcinoma. Our results are likely attributable to the routine application of our treatment protocol.

INTRODUCTION

With advances in surgical techniques and perioperative care, there has recently been a great improvement in the results of liver resection. For hepatocellular carcinoma (HCC), one of the most common malignancies worldwide, perioperative mortality rates of around 5% are frequently reported (1-3), and many liver surgeons seem to consider these rates acceptable. However, recent studies from specialized medical centers have reported zero mortality rates (4,5). It is therefore important that we re-evaluate the safety of liver resection in patients with HCC.

Hepatic resection has long been held to be the only potentially curative option for HCC. The long-term outcome of 'curative' resection is, however, far from satisfactory because of the high incidence of intrahepatic recurrence (6,7). To improve the surgical outcome of HCC patients, we need to establish effective treatment strategies for such recurrences.

During the last 11 years we have routinely applied our own treatment protocol to HCC patients, which consists of a set of selection criteria for hepatectomy (8,9), combined with surgical techniques aimed at minimizing intraoperative blood loss (9-11), careful follow-up, and an aggressive surgical approach for recurrence (12,13). Using this protocol, we have performed 324 initial and 80 repeat hepatectomies, including 18 third and two fourth resections. Here, we review our 11-year experience of liver resection for HCC and clarify the safety and potential benefits of hepatectomy.

METHODOLOGY

Between January 1990 and December 2001, we have performed 404 potentially curative hepatectomies: 324 initial and 80 repeat liver resections, on 337 HCC patients at the First Department of Surgery, Shinshu University. Potentially curative resection means removal of all gross tumors. These 337 patients, including 13 patients who underwent their initial (8 patients) or second hepatectomy (5 patients) at other institutions, are the subjects of this report. There were 258 men and 79 women, and their mean age was 64 years (range, 21- 85 years). The type of liver resection was defined according to the scheme shown in **Figure 1** (8). If ascites could not be controlled with diuretics preoperatively, liver resection was not indicated. The serum bilirubin value and the indocyanine green retention rate at 15 minutes (ICG-R) were the major parameters for determining the extent of resection. The details of the surgical tech-

Hepato-Gastroenterology 2006; 53:736-741

Original Paper

Perioperative Hemodynamic Study of Patients Undergoing Abdominal Surgery using Pulse Dye Densitometry

Masanori Nishioka MD[1], Masashi Ishikawa MD, PhD[2], Norikazu Hanaki MD[1] Yutaka Kashiwagi MD, PhD[2], Hisashi Miki MD, PhD[2], Hidenori Miyake MD, PhD[1] Seiki Tashiro MD, PhD[1]

[1]Department of Digestive Surgery, University of Tokushima, School of Medicine and [2]Department of Surgery, National Kochi Hospital, Japan

Corresponding Author: Masanori Nishioka, MD, Department of Digestive Surgery, University of Tokushima School of Medicine, 1-50-2 Kuramoto cho, Tokushima City, 770-8503 Japan

Tel: +81 88 631 3111, Fax: +81 88 631 9698, E-mail: khotchi@clin.med.tokushima-u.ac.jp

KEY WORDS: Pulse dye densitometry; Hemodynamic change; Digestive surgery

ABBREVIATIONS: Pulse Dye Densitometry (PDD); Indocyanine-Green (ICG); Cardiac Output (CO); Cardiac Index (CI); Blood Volume (BV); ICG elimination rate (K-ICG); Postoperative Day (POD); Systemic Inflammatory Response Syndrome (SIRS)

ABSTRACT

Background/Aims: Pulse dye densitometry (PDD) using indocyanine-green (ICG) is a newly developed technique for monitoring cardiac output (CO), cardiac index (CI), circulating blood volume (BV) and ICG elimination rate (K-ICG). We measured hemodynamic changes during the perioperative period in patients undergoing digestive surgery to analyze relationships between hemodynamic changes and surgical procedures, blood loss, water balance and SIRS.

Methodology: Eighty-seven patients who underwent gastrectomy (n=46) and colectomy (n=41) without postoperative complications were enrolled in this study. The corresponding data from 15 patients who underwent laparoscopic cholecystectomy were used as controls. CO, CI, BV and K-ICG were measured by PDD before operation, on the first postoperative day (POD 1), POD 3, POD 7 and POD 14.

Results: In all patients, CO and CI increased significantly until POD 3 compared with preoperative levels. BV on POD 1 decreased significantly compared to the preoperative level. K-ICG increased significantly until POD 14. Laparoscopic cholecystectomy resulted in less surgical stress than gastrectomy or colectomy as measured by hemodynamic changes. There were minimal differences in hemodynamics between the gastrectomy and colectomy groups. There were significant negative correlations between intraoperative blood loss and the [POD 1: preoperative values] ratios for CO, CI, BV or K-ICG. There was no correlation between changes in water balance from operation to POD 1 and [POD 1: preoperative value] BV ratio.

Conclusions: An increase in CO and decrease in BV were observed at the early operative stage, especially in patients with systemic inflammatory response syndrome (SIRS). Interestingly, hepatic artery flow volume (K-ICG) remained high until POD 14. It is important to minimize intraoperative blood loss, since it markedly affects postoperative hemodynamics.

INTRODUCTION

The importance of monitoring hemodynamic changes in critically ill patients during perioperative management is widely recognized and many methods have been developed to monitor these changes. Conventionally, the Swan-Ganz method has been used to evaluate hemodynamic changes in ICU patients. However, it is invasive and is complicated to perform at the bedside (1-3). Pulse dye densitometry (PDD), a method newly developed by Aoyagi *et al.*, provides a noninvasive means for repeated measurements of cardiac output, cardiac index, circulating bloody volume by determining the indocyanine green elimination rate (K-ICG) following injection ICG into a peripheral vein (4,5). The accuracy and reproducibility of this method in estimating cardiac output and blood volume in comparison to the Swan-Ganz method and radioisotope method has been confirmed by other reports (6-15). Measurements of circulating blood volume may be of particular value in circumstances in which acute hemodynamic changes can potentially occur, for example in sepsis and major surgery. After cardiac surgery during which there was extracorporeal circulation with hemodilution, it is well understood that BV decreases while water accumulates in the interstitial space (16). However, repeated measurements of cardiac output and blood volume at the bedside of critically ill patients is unfeasible, therefore, potential hemodynamic changes in such patients have only been the subject of speculation. Information on hemodynamic change would be beneficial for management of patients experiencing cardiac or other complications. Until now, reports on perioperative hemodynamic change following digestive surgery have been very limited.

The first purpose of the present study is to investigate the perioperative hemodynamic changes by PDD using ICG in relation to type of surgical procedures in patients undergoing digestive surgery. Prolonged

Hepato-Gastroenterology 2006; 53:874-878

hypoperfusion of the gut and liver during operation are reported to lead to severe complications and an increased mortality rate in resuscitation from hemorrhagic shock (17). Although correction of volume depletion is the main method of resuscitation, the methods used vary widely and are dependent on clinician's experience. The second purpose of this study is to analyze relationships between hemodynamic change and operative factors such as blood loss and perioperative water balance.

Systemic inflammatory response syndrome (SIRS) describes a clinical response arising from non-specific insult, but it also includes a number of pathologic states because of its loose definition. Although patients with major surgeries show high rates of postoperative SIRS, it is transient, followed by complete recovery, in 1 to 3 days. However, little is known about differences in hemodynamic changes between postoperative SIRS and non-SIRS patients. Hence, the third purpose of this study is to evaluate differences in hemodynamic changes in such patients during the early postoperative stage.

METHODOLOGY

Patient Population and Data Collection

From May 1999 through March 2001, 87 patients who underwent gastrectomy for gastric cancer [n=46, 31 men and 15 women aged 64±13 years (mean ±SD)], colectomy for colorectal cancer (n=41, 20 men and 21 women aged 68±16 years) at the Department of Surgery, National Kochi Hospital were enrolled in this prospective study. The control group consisted of 15 patients who underwent laparoscopic cholecystectomy for cholecystolithiasis (7 men and 8 women aged 53±16 years). All experimental protocols were approved by the Research Committee of National Kochi Hospital. Exclusion criteria were as follows: serious hepatic dysfunction, coexisting severe cardiovascular and pulmonary disease, requirement for mechanical ventilation, and postoperative complications. The heights of the subjects ranged from 135 to 177cm (mean 158±10cm) and their body weights varied from 22 to 84kg (55±12kg). Cardiac output (CO), cardiac index (CI), circulating blood volume (BV) and K-ICG were measured five times; preoperatively, and on postoperative days (POD) 1, 3, 7, and 14. Measurements were performed by pulse dye densitometry with indocyanine-green (DDG-2001, Nihon Kohden Corp., Tokyo, Japan). All patients were studied while resting in bed, and measurements were taken in the morning before other examinations. Measurements of CO, CI and BV were calculated as described previously. Briefly, a probe was secured on one nostril or finger, and after sampling blood to measure hemoglobin, 20mg ICG was injected via an antecubital venous line while DDG was recorded for 10 min.

Pulse dye densitometry is based on the principle of pulse spectrophotometry. Wavelengths of 805 and 890nm were used to measure the ratio of blood ICG concentration to hemoglobin concentration. Because the extinction coefficient of ICG in blood is at its maximum at 805nm and is almost zero at 890nm, and the difference in oxyhemoglobin and reduced hemoglobin extinction coefficients at these wavelengths is negligibly small, ICG concentration can be calculated from the ratio of its concentration to total hemoglobin concentration for each pulse. In addition, the elimination rate constant (K) of ICG (K-ICG), which is equivalent to hepatic blood flow, is calculated by ICG elimination curve as detected with a DDG analyzer (6-13).

As defined by ACCP/SCCM consensus conference in 1992, SIRS was diagnosed if 2 or more of the criteria were met (18). Forty-three patients (23 gastric resections and 18 colorectal resections) exhibited SIRS on POD 1, whereas 44 patients showed no sign of postoperative SIRS on POD 1. On POD 3, there were 19 patients with SIRS and 68 patients without SIRS. No patients in the laparoscopic cholecystectomy group developed SIRS.

Surgical Management

All patients received the general anesthetic sevoflurane by endotracheal inhalation while the gastrectomy and cholecystectomy groups additionally received epidural anesthesia. Laparoscopic cholecystectomy was performed by the abdominal wall lifting method, gastrectomy with D1 or D2 lymph node dissection as described in the second English edition of the *Japanese Classification of gastric carcinoma* and colectomy with D2 or D3 lymph node dissection as described in the *Japanese Classification of colorectal carcinoma.* Epidural analgesia was provided before surgery and maintained for 72 hours postoperatively as analgesia. Perioperatively, continuous intravenous fluid resuscitation was given to maintain urine output (>1.0mL/kg per hr). We performed blood transfusion and infusion of hydroxyethylstarch solution based on the volume of blood loss during and/or after surgery. The mean estimated operative blood loss was 261±265mL for the gastrectomy group, 301±375mL for the colectomy group and 73±134mL for the laparoscopic cholecystectomy group (range; 0-1580mL). Two patients (gastrectomy and colectomy) received blood transfusions intraoperatively. The mean estimated operation time was 229±51 min for the gastrectomy group, 228±91 min for the colectomy group and 128±54 min for the laparoscopic cholecystectomy group (range; 65-630 min). Patients received intravenous fluid in amounts ranging from 450 to 4620mL (mean 1604±848mL). The intraoperative mean total water balance, namely the average amount of drip infusion and urine production including blood balance, was 1118±639mL (range; 115-2795mL). None of the patients received steroids, low-dose dopamine or selective gut decontamination. Antibiotics were administered according to a predetermined protocol that was modified if specific microbiologic information became available. No patient received enteral nutrition during the study.

Statistical Analysis

Unless otherwise noted, data values are presented as mean ± SD. The statistical significance of difference between data was assessed with Student's paired t test. Linear regression analysis was used to determine the relationships between intraoperative blood loss and hemodynamic changes, and between water balance and BV. Calculations were performed using the statistical software package Stat View (Abacus Concepts, Berkeley, CA). A p value of less than 0.05 was considered significant.

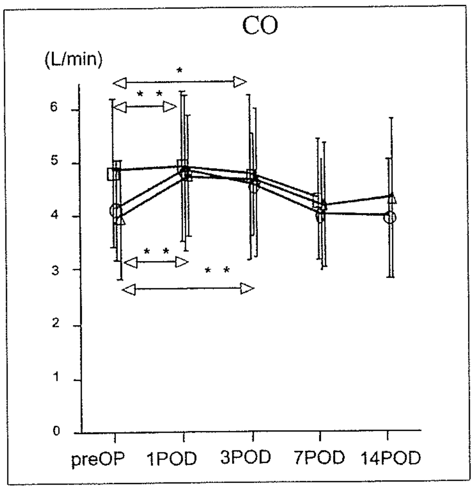

FIGURE 1
Changes in cardiac output (CO) and cardiac index (CI) in surgical patients. There were significant increases in CO and CI until POD 3 compared with preoperative levels.

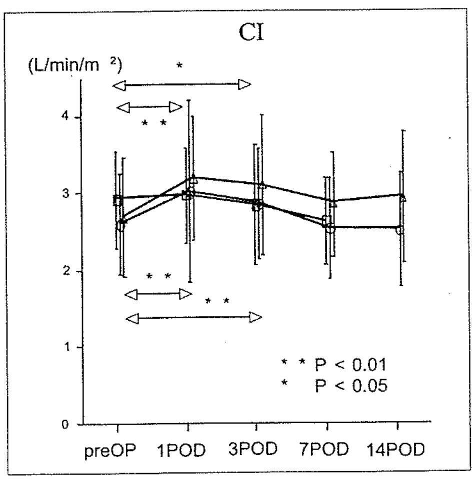

FIGURE 2
Changes in cardiac output (CO) (●; gastrectomy, □; colectomy, ○; Laparoscopic cholecystectomy). An increase of CO in gastrectomy and colectomy groups was seen until POD 3 despite no significant changes in the laparoscopic cholecystectomy group.

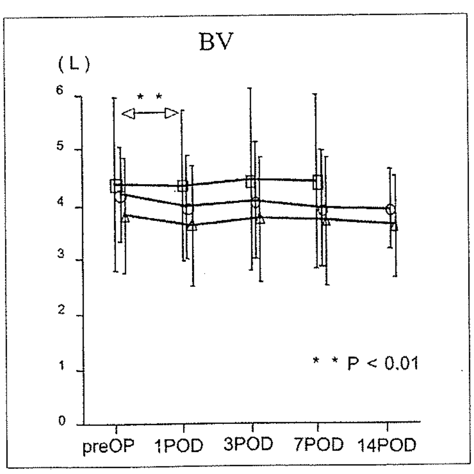

FIGURE 3
Changes in circulating blood volume (BV) (●; gastrectomy, □; colectomy, ○; Laparoscopic cholecystectomy). A decrease of BV in gastrectomy group was seen until POD 1 despite no significant changes in the colectomy and laparoscopic cholecystectomy groups.

RESULTS

In the gastrectomy and colectomy groups, the mean CO and CI values increased significantly until POD 3 compared with their preoperative values (CO: 4.8±1.3 on POD 1 and 4.6±1.2 on POD 3 *vs.* 4.0±1.0 L/min before operation, CI: 3.1±1.0 on POD 1 and 3.0±0.8 on POD 3 *vs.* 2.6±0.7 L/m^2 before operation) **(Figure 1)**. The values at any time point were not significantly different between the gastrectomy and colectomy group. No significant postoperative changes were observed in CO and CI in the laparoscopic cholecystectomy group **(Figure 2)**. The mean preoperative BV value for the gastrectomy group was 74±17mL/kg, which significantly decreased to 69±18mL/kg on POD 1 and immediately recovered to 71±18mL/kg on POD 3 **(Figure 3)**. No significant decreases in BV were observed in the colectomy or laparoscopic cholecystectomy groups. The K-ICG value increased significantly until POD 3 for the laparoscopic cholecystectomy group, until POD 7 for the gastrectomy group and until POD 14 for the colectomy group **(Figure 4)**. There were significant negative correlations between intraoperative blood loss and the [POD 1/preoperative value] ratios for CO, CI, BV or K-ICG. There was a correlation between the [POD 1/preoperative value] CO ratio and intraoperative blood loss ($R=0.38$, $p=0.001$) **(Figure 5)**. All subjects who developed intraoperative blood loss of over 700mL showed a decrease in CO on POD 1 as compared with their preoperative value. The correlation coefficients of the [POD 1/preoperative value] CI ratio and BV ratio to intraoperative blood loss were 0.38 ($p=0.001$) and 0.42 ($p<0.0001$), respectively. All patients who developed blood loss of over 700mL showed a decrease in BV as well as changes in CO. A moderate correlation was also seen between intraoperative blood loss and the [POD 1/preoperative value] K-ICG ratio ($R=0.29$, $p=0.01$). There was no correlation between changes in water balance from operation to POD 1 and the ratio [POD 1/preoperative value] for CO, CI, BV and K-ICG.

Although CI on POD 3 in patients with postoperative SIRS was significantly higher than in patients without postoperative SIRS (3.4±0.9 *vs.* 2.84±0.8, $p<0.01$), no significant differences in BV and K-ICG levels were seen between the two groups.

DISCUSSION

The normal physiological response to stress and injury results in a series of cardiovascular changes including increases in heart rate, heart contractility and cardiac output. However, little is known about alterations in BV and hepatic blood flow volume. The present study shows that in patients who undergo gastrectomy or colectomy, CO, CI and K-ICG increase in the early postoperative stage despite a decrease in BV. This indicates a hyperdynamic postoperative state. However, CO, CI and BV return to their preoperative levels soon after surgery (POD 1 for BV and POD 3 for CO and CI). Judging from these findings, cardiac output transiently increases immediately after gastrectomy and colectomy while hepatic artery flow volume shows a prolonged increase, and BV a transient decrease. It was also noted that K-ICG remains significantly higher than the preoperative value until POD 14, despite the return of CO, CI and BV to baseline levels.

Generally, in humans a crisis of depletion of BV is resolved by centralization of BV. The increase in K-ICG observed in the present study may be induced by centralization of BV in response to surgical stress. It has been reported that portal vein blood flow decreases after major abdominal surgeries (19). However, Kennedy *et al.* reported that estimated hepatic blood flow decreases significantly, as much as 23%, after high spinal anesthesia and that this decrease is associated with a reduction in mean arterial pressure. Additionally, no significant alteration in cardiac output or splanchnic vascular resistance was observed, and the fraction of cardiac output delivered to the splanchnic circulation was significantly reduced by 21% (20).

Circulating blood volume is a constantly changing parameter because of blood pooling in the spleen, liver and other organs. Further, it has been suggested that during strenuous conditions the spleen might release pooled erythrocytes to the general circulation (21). Correction of the volume depletion is the main therapy of resuscitation in hemorrhagic shock. In general, BV can be controlled by infusion of fluids such as a hydroxyethylstarch solution (22). In the present study, we observed no correlation between water balance and the [POD 1: preoperative value] BV ratio, indicating that fluid therapy may be insufficient for controlling circulating blood volume during the perioperative period. We also found that it is important to reduce intraoperative bleeding and surgical stress to maintain postsurgical hemodynamic stability; patients significant intraoperative blood loss tend to have decrease of BV at the early postoperative stage. Volume-deficit hypovolemia seems to be a crucial factor for determination of prognosis in various clinical settings. Shoemaker *et al.* reported that more than half of critically ill patients had a volume deficit of 0.5-2.0 L (23). BV monitoring using a DDG analyzer may help to identify such a volume deficit and act as a guide for fluid therapy. Most studies regarding BV have been performed in healthy individuals, while the present study was performed on patients undergoing abdominal surgery. To our knowledge, the present study is one of the first reports regarding BV monitoring in patients with abdominal surgery using the PDD method. It has been reported that hypovolemia can be predicted from a postoperative decrease in serum sodium. Hyponatremic hypovolemia may be induced by shift of fluid and sodium to the interstitial space due to surgical stress (24). Rothe *et al.* reported that BV decreased by nearly 30% in an endotoxin infusion model, suggesting a shift of intravascular blood to the extracellular space (25). Our study confirms that intraoperative blood loss effects hemodynamic changes (CO, CI, BV or K-ICG) on POD 1. Henry *et al.* reported that the hemorrhage of an amount representing 15 to 20% of the estimated blood volume produced significant reductions in splanchnic blood volume. Half of the blood lost was contributed by the splanchnic viscera, which lost roughly 40% of initial volume. In contrast, central blood volume was depleted by only 10% and cardiac output was unaltered (26).

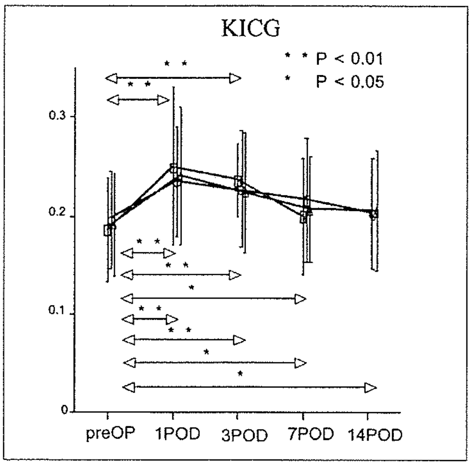

FIGURE 4
Changes in ICG elimination rate (K-ICG) (●-●; gastrectomy, □-□; colectomy, ○-○; Laparoscopic cholecystectomy). The value of K-ICG increased significantly in the laparoscopic cholecystectomy, gastrectomy, and colectomy groups until POD 3, 7, and 14, respectively.

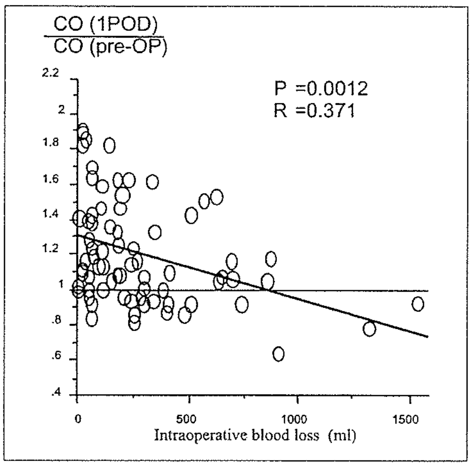

FIGURE 5
Correlation between the [POD 1/preoperative value] CO ratio and intraoperative blood loss in patients undergoing gastrectomy and colectomy. There was a correlation between CO ratio and intraoperative blood loss ($R=0.38$, $p=0.001$).

In relationships between surgical procedures and hemodynamic changes, there are hardly any differences between gastrectomy and colectomy. Although it is generally recognized that laparoscopic cholecystectomy is less invasive than the open procedures (27), no studies regarding measuring hemodynamics through POD 14 have been performed. Our findings that CO, CI and BV values do not change following laparoscopic cholecystectomy supports the belief that laparoscopic cholecystectomy results in less surgical stress and fewer hemodynamic changes. Nevertheless K-ICG remains high until POD 3 in laparoscopic cholecystectomy patients, suggesting that centralization of BV occurs even under conditions of less surgical stress such as laparoscopic cholecystectomy. In only the gastrectomy group, postoperative BV decreased significantly on POD 1 compared with preoperative value, thus particular attention should be paid to decreased BV following gastrectomy. Adequate circulatory management should be provided to patients according to surgical method. We suggest that accumulation of more data using the PDD monitoring system will reveal the utility of BV in estimating the amount of surgical stress resulting from various major abdominal surgeries.

A large multidisciplinary research effort has so far focused on the pathophysiologic response to diverse processes ranging from SIRS to severe sepsis. Postoperative SIRS, which was examined in the present study, was developed to indicate a clinical response arising from a surgical procedure rather than infection. The current study showed that the cardiac index increased until 3 days after surgery with a significant increase in patients with postoperative SIRS compared with patients without postoperative SIRS. However, postoperative changes in BV and K-ICG values showed no significant differences between the SIRS group and non-SIRS group.

Furthermore, most subjects with postoperative SIRS possessed an increased heart rate. Judging from the present findings, it is suspected that postoperative SIRS results in a hyperdynamic state consisting of increased heart rate and stroke volume, but exhibiting little differences in changes of blood volume and hepatic blood flow volume between the two groups. Further work is needed to characterize the clinical and hemodynamic importance of SIRS.

CONCLUSIONS

With the ICG PDD method, we have more accurately characterized the hemodynamic changes that occur after major abdominal surgery. It is important to reduce intraoperative bleeding because blood loss negatively affects hemodynamic stability in the early postoperative stage. As well, more attention should be paid to perioperative hemodynamic changes in patients undergoing gastrectomy and colectomy so proper treatments can be administered. Further studies are needed to evaluate strategy to properly manage patients with complications resulting from major surgeries.

REFERENCES

1 **Eagle K, Brundage B, Chaitman B, et al:** Guidelines for perioperative cardiovascular evaluation of the noncardiac surgery. A report of the American Heart Association/American College of Cardiology Task Force on assessment of diagnostic and therapeutic cardiovascular procedures. Circulation 1996; 93:1278-1317.

2 **Baek SM, Makabali GG, Bryan-Brown CW, et al:** Plasma expansion in surgical patients with high central venous pressure (CVP); the relationship of blood volume to hematocrit, CVP, pulmonary wedge pressure and cardiorespiratory changes. Surgery 1975; 78:304-315.

3 **Pulmonary artery catheter consensus conference participants:** pulmonary artery catheter conference: consensus statement. Crit Care Med 1997; 25:910-925.

4 **Aoyagi T, Miyasaka K:** Pulse oximetry and its simulation. Densi Tokyo (IEEE Tokyo Section) 1990; 29:184-187.

5 **Aoyagi T, Fuse M, Kanemoto M, et al:** Pulse dye-densitometry. Jpn J Clin Monit 1994; 5:371-379. (In Japanese with English abstract)

6 **Iijima T, Aoyagi T, Iwao Y, et al:** Cardiac output and circulating blood volume analysis by pulse dye-densitometry. J Clin Monit 1997; 13:81-89.

7 **Imai T, Takahashi K, Fukura H, et al:** Measurement of cardiac output by pulse dye densitometry using indocyanine green. Anesthesiology 1997; 87:816-822.

8 **Haruna M, Kumon K, Yahagi N, et al:** Blood volume measurement at the bedside using ICG pulse spectrophotometry. Anesthesiology 1998; 89:1322-1328.

9 **Iijima T, Iwao Y, Sankawa H:** Circulating blood volume measured by pulse dye-densitometry: comparison with 131I-HSA analysis. Anesthesiology 1998; 89:1329-1335.

10 **He YL, Tanigami H, Ueyama H, et al:** Measurement of blood volume using indocyanine green measured with pulse-spectrophotometry: Its reproducibility and reliability. Crit Care Med 1998; 26:1446-1451.

11 **Imai T, Takahashi K, Goto F, et al:** Measurement of blood concentration of indocyanine green by pulse dye densitometry-comparison with the conventional spectrophotometric method. J Clin Monit Comput 1998; 14:477-484.

12 **Barker SJ:** Blood volume measurement: The next intraoperative monitor? Anesthesiology 1998; 89:1310-1312.

13 **Watanabe Y, Kumon K:** Assessment of pulse dye-densitometry indocyanine green (ICG) clearance test of hepatic function of patients before cardiac surgery: its value as a predictor of serious postoperative liver dysfunction. J Cardiothorac Vasc Anesth 1999; 13:299-303.

14 **Busse MW, Zisowski S, Henschen S, et al:** Plasma volume estimation using indocyanine green. Anesthesia 1993; 48:41-43.

15 **Imai T, Mitaka C, Nosaka T, et al:** Accuracy and repeatability of blood volume measurement by pulse dye densitometry compared to the conventional method using 51 Cr-labeled red blood cells. Intensive Care Med 2000; 26:1343- 1349.

16 **Bracco D, Revelly JP, Berger MM, et al:** Bedside determination of fluid accumulation after cardiac surgery using segmental bioelectrical impedance. Crit Care Med 1998; 26:1065-1070.

17 **Nordin A, Makisalo H, Hockerstedt K:** Dopamine infusion during resuscitation of experimental hemorrhagic shock. Crit Care Med 1994; 22:151-156.

18 **Members of the American College of Chest Physicians/Society of Critical Care Medicine consensus conference committee. American College of Chest Physicians/Society of Critical Care Medicine consensus conference committee:** Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992; 20:864-874.

19 **Meier-Hellmann A, Reinhart K, Bredle D, et al:** Epinephrine impairs splanchnic perfusion in septic shock. Crit Care Med 1997; 25:399-404.

20 **Kennedy WF, Everett GB, Cobb LA, et al:** Simultaneous systemic and hepatic hemodynamic measurements during high spinal anesthesia in normal man. Anesth Analg 1970; 49:1016-1024.

21 **Laub M, Hvid-Jacobson K, Hovind P, et al:** Spleen emptying and venous hematocrit in humans during exercise. J Appl Physiol 1993; 74:1024-1026.

22 **Ueyama H, He YI, Tanigami H, et al:** Effects of crystalloid and colloid preload on blood volume in the parturient undergoing spinal anesthesia for elective cesarean section. Anesthesiology 1999; 91:1571-1576.

23 **Shoemaker WC, Kram HB, Appel PL:** Therapy of shock based on pathophysiology, monitoring, and outcome prediction. Crit Care Med 1990; 18:19-25.

24 **Hirasawa K, Kasuya H, Hori T:** Change in circulating blood volume following craniotomy. J Neurosurg 2000; 93:581-585.

25 **Rothe CF, Murray RH, Bennett TD:** Activity circulating blood volume in endotoxin shock measured by indicator dilution. Am J Physiol 1979; 236:H291-300.

26 **Price HL, Deutsch S, Marshall BE, et al:** Hemodynamic and metabolic effects of hemorrhage in man, with particular reference to the splanchnic circulation. Circ Res 1966; 18:469-474.

27 **Goodale RL, Beebe DS, McNevin MP, et al:** Hemodynamic, respiratory, and metabolic effects of laparoscopic cholecystectomy. Am J Surg 1993; 166:533-537.

Surg Today (2006) 36:410–415
DOI 10.1007/s00595-005-3177-2

SURGERY TODAY

Original Articles

Creating a Manual for Proper Hand Hygiene and Its Clinical Effects

SHINYA KUSACHI, YOSHINOBU SUMIYAMA, YOUICHI ARIMA, YUICHI YOSHIDA, HIDENORI TANAKA, YOUICHI NAKAMURA, JIRO NAGAO, YOSIHISA SAIDA, MANABU WATANABE, and JUNKO SATO

Third Department of Surgery, Toho University School of Medeicine, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan

Abstract

Purpose. To prevent cross-infections, we created a manual for the treatment of infectious wounds that clarifies when to wash one's hands and when to wear gloves.

Methods. Six patients with widespread infectious wounds caused by methicillin-resistant *Staphylococcus aureus* (MRSA) were treated. The bacterial count on the hands of the staff was calculated. We then compared the number of patients with MRSA isolated, and typed the MRSA isolates using pulsed-field gel electrophoresis (PFGE).

Results. The pathogenic bacterial count among hospital staff before treatment/before hand hygiene was 8.2×10 colony-forming units (cfu)/hand, which were not detected before treatment/after hand hygiene. The pathogenic bacterial count on the hands before hand hygiene/after treatment climbed to 9.1×10^5 cfu/hand, and after treatment/after hand hygiene decreased to 0.38 cfu/hand. The number of patients with MRSA isolates before this protocol was 15/402 (3.7%), but that level significantly decreased to 5/411 (1.2%) after implementation of the manual. There were 13 strains of type F by PFGE before the manual was adopted, but five strains of MRSA isolated after the present manual was enforced were all observed to have different migration patterns.

Conclusion. A hand hygiene manual is effective for decreasing the rate of cross-infection.

Key words Surgical site infection · Infected wound · Cross infection · Methicillin-resistant *Staphylococcus aureus* · Hospital infection · Hand hygiene

Reprint requests to: S. Kusachi
Received: April 23, 2004 / Accepted: November 15, 2005

Introduction

It is clear that hand hygiene is the most fundamental technique for preventing hospital infection. The Centers for Disease Control (CDC) recently published a manual on hand hygiene that recognizes the efficacy of and broadly recommends washing the hands with a disinfectant containing alcohol, in addition to a detergent and water as conventionally recommended.[1–3] However, when treating patients with infectious wounds, infection transmission via hand/wound contact by medical personnel is still likely to occur. The CDC recommends wearing gloves when coming into contact with all patient blood, feces, and secreta except for perspiration, and it also recommends thorough hand hygiene.[4,5] However, cross-infection cannot be prevented simply by hand hygiene after treatment. There is still the risk of contamination while physically moving to the next patient who requires treatment, and from contact with other medical utensils during treatment.

The decision on when to wash one's hands during the treatment of infectious sores is made by each individual medical member of staff. As a result of this inconsistent approach, cross-infection can occur due to inadequate hand hygiene, while too much washing of hands can cause contact dermatitis in the attending personnel.[6,7] To prevent hospital staff members from transferring pathogenic bacteria from previously treated patients to patients waiting for treatment, we created a manual for the treatment of infectious wounds that clarifies when to wash the hands and when to wear gloves. By following this manual it was possible to prevent a cross-infection in surgical wards during the study period. We herein report on the hand bacterial count of the treating staff during wound treatment and the number of patients with methicillin-resitant *Staphylococcus aureus* (MRSA) isolates, and also on the analysis of these MRSA isolates as demonstrated by pulsed-field gel electrophoresis (PFGE).

Table 1. Hand hygiene manual for the treatment of surgical wounds: timing of hand scrubbing and treatment handling

- Scrubbing of the hands is not necessary when entering the patient's room, pulling in the dressing trolley, and approaching the patient's bedside
- Once the dressing treatment preparation has been complete, the treating staff and caring staff should scrub their hands
- Caring staff or treating staff remove the patient's sleep wear and undo any abdominal bandage
- Treating staff put on gloves and remove dressings, and treat the wound
- All nonhygienic tasks are performed by the treating staff
- The treating staff cover the wound with dressing, then the nurse applies taping, etc.
- The treating staff place nonhygienic material in an infectious waste container, remove their gloves, and finally scrub their hands
- The caregiver scrubs his/her hands
- The next patient is visited

The manual advises when treating and caring staff should wash their hands, and when they should wear gloves when treating infectious wounds. This schedule assumes the use of a trolley when the dressing is changed

Table 2. Changes in the incidence of patients with isolated methicillin-resistant *Staphylococcus aureus* (MRSA)

	Incidence of MRSA infection
Before the manual	3.7% (15/402)
After the manual	1.2% (5/411)*

*$P < 0.005$

Subjects and Methods

The procedure used for treating the infected wounds was developed in accordance with the manual shown in Table 1. All staff members washed their hands with a 70% alcohol-based antiseptic called "waterless antiseptic."

Bacteriological Investigation

Twenty-one surgeons and seven nurses treated six patients 21 times over 3 days. The patients were hospitalized in the gastroenterology/general surgery wards of the Toho University School of Medicine Ohashi Hospital (now Toho University Medical Center Ohashi Hospital) and they presented with a broad range of MRSA-infected wounds. The physicians treated the wounds and the nurses were responsible for all aftercare. The changes in hand the bacterial count during these treatments were measured using a palm stamp (Eiken Chemical, Tokyo, Japan). The hand bacterial count was measured four times, namely before treatment, after hand hygiene before treatment, before hand hygiene after treatment, and after hand hygiene after treatment. Before hand hygiene after treatment, the hand bacterial count was measured while gloves were being worn. In the calculation of the bacterial count, MRSA, *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterococcus* spp., *Klebsiella* spp., and *Enterobacter* spp. on the hands were counted as pathogenic bacteria, while *Staphylococcus aureus*, *Streptococcus epidermidis*, and hemolytic *Streptococcus* were regarded as indigenous skin bacteria.

Investigation by PFGE

The MRSA obtained from all MRSA-infected patients for a period of 6 months before and 6 months after the start of implementation of the present method was typed by PFGE, and the presence or absence of cross-infection was investigated.

Clinical Investigation

For the clinical investigation, the rate of postoperative MRSA infections (per number of operations) in the same ward from May 1997 to April 1998 (before the implementation of the manual) and from May 1998 to April 1999 (after the implementation of the manual), and the MRSA infection rate for 6 months after implementation, were all compared. Furthermore, the MRSA obtained from all MRSA infected patients in the 6 months before the implementation of the technique and in the 6 months after the implementation of the technique was typed by PFGE and the presence or absence of cross-infection investigated. The chi-square test was performed for a statistical analysis, and significance was defined as $P < 0.05$.

Results

Bacteriological Investigation

The hand bacterial count was compared between the treating staff and the caring staff (Fig. 1). The total bacterial count on the hands — before hand washing before treatment — for the treating staff was 3.4 × 10 (5 colony-forming units [cfu]/hand), of which 8.2 × 10

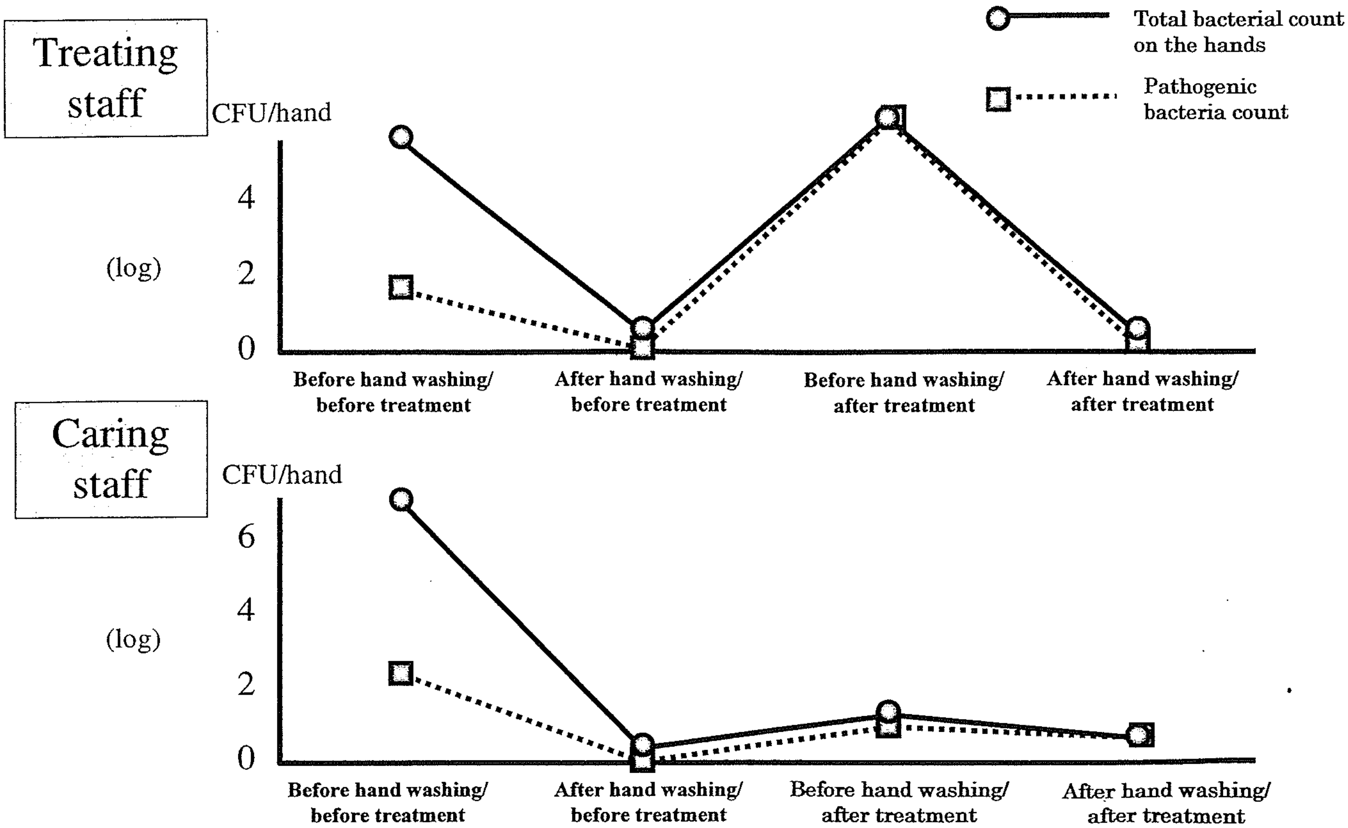

Fig. 1. Changes in hand bacterial count. By disinfecting the hands before and after treatment, the transfer of pathogenic bacteria from patient to patient was prevented. By washing the hands after treatment, pathogenic bacterial transmission to the next patient to be treated was thus prevented

(1 cfu/hand) were pathogenic bacteria. The total bacterial count on the hands of the treating staff after hand washing before treatment decreased to 2.9 cfu/hand, and no pathogenic bacteria were detected. Before hand washing after treatment the bacterial count on the hands of the treating staff increased to 9.1 × 10 (5 cfu/hand) and all were pathogenic bacteria. After hand washing after treatment, the total bacterial count was 1.5 cfu/hand, of which 0.38 cfu/hand were pathogenic. Both before and after treatment, the bacterial count decreased significantly after hand washing. The total hand bacterial count — before treatment and before hand disinfection — of the caring staff was 9.5 × 10 (6 cfu/hand), of which 1.8 × 10 (2 cfu/hand) were pathogenic bacteria. The total hand bacterial count of the caring staff after hand washing before treatment decreased to 1.6 cfu/hand, and no pathogenic bacteria were detected. In any event, the bacterial count significantly decreased compared to before treatment/before hand washing. Before hand washing after treatment, the bacterial count of the caring staff increased to 5.1 × 10 cfu/hand, of which 3.4 × 10 cfu/hand were pathogenic, but not significant compared to before treatment/before hand washing. After hand washing after treatment, the total hand bacterial count was 3.4 cfu/hand, and all bacteria were pathogenic. There were no significant differences in the hand bacterial count of the treating staff between after treatment/before hand disinfection and after treatment/after hand disinfection. A comparison of the treating staff and caring staff revealed a significantly high pathogenic bacterial count among the treating staff after treatment/before hand washing.

Investigation by PFGE

During this period, when the MRSA obtained from the MRSA-infected patients was typed by PFGE, there was one strain each of type D and type E MRSA before this program was conducted, and all the remaining 13 strains were type F (Fig. 2). Five strains of MRSA isolated after the present manual was adopted were all seen to have different migration patterns, which thus ruled out cross-infection.

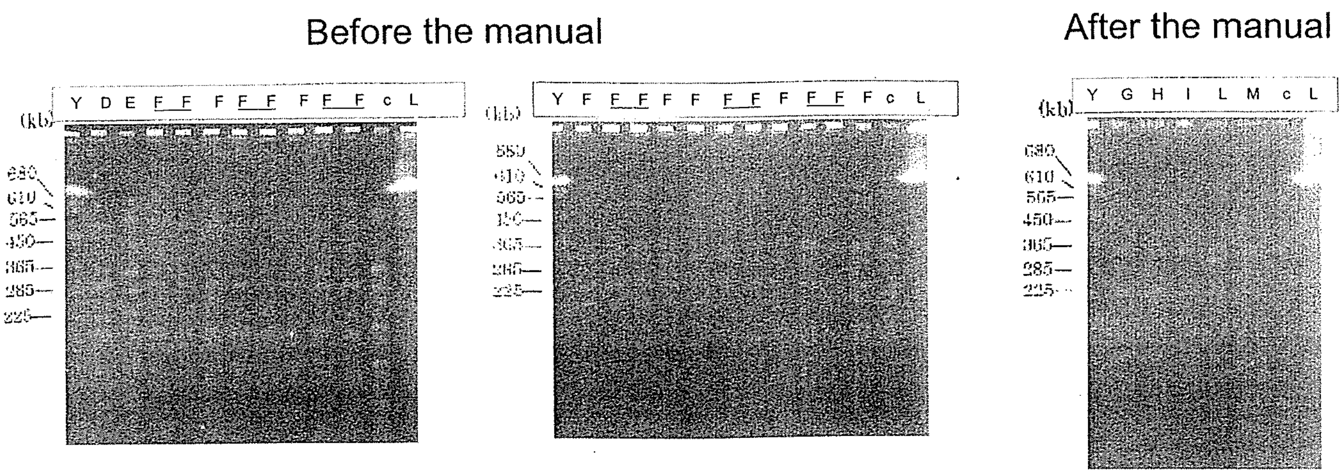

Fig. 2. Classification of MRSA type by pulsed-field gel electrophoresis (PFGE). Before the introduction of the hand hygiene manual the same strain was conspicuous, but after the manual's introduction, different types of MRSA were isolated

Clinical Investigation

The number of patients with MRSA isolates in the year before this program was implemented was 15/402 (3.7%), but the number of patients with MRSA isolates in the year after implementation significantly decreased to 5/411 (1.2%).

Discussion

It is clear that the prevention of infection via medical personnel hand contact is the most important factor for dealing with hospital infection. As a guideline for hand hygiene, the CDC approved washing the hands with detergent and running water as per convention and then washing the hands by rubbing them with hand antiseptic as a new step in hand hygiene.[1-3] Since the rapid rise of MRSA infections in the late 1980s, measures against hospital infection, and particularly measures to combat contact infection via the hands of medical personnel, have been conducted throughout Japan.[8] Manuals on combating hospital infections in the West have been introduced, and it has become clear that there is little point in changing shoes in the operating room and intensive care unit and in disinfecting absorbent floor mats and the patient environment, as have conventionally been practiced in Japan. With regard to wound treatment also, such methods such as abolishing the dressing trolley and using pack-style dressing have also been adopted in some hospitals. However, although the risk of the dressing trolley becoming contaminated has been pointed out, many types of dressings are now required for patients with broad-ranging infectious wounds that secrete a considerable amount of secreta. As a result, some type of trolley is necessary for transporting disinfectant or cleaning equipment to the bedside. Treatment products that were unanticipated can also at times become required and the use of a dressing trolley is extremely convenient considering the time it takes to visit the materials room each time. A dressing trolley is also a very convenient, clever way of collecting infectious waste or dressing materials containing such infectious waste so as to prevent contamination of the surrounding environment. From this point of view, it would be difficult to treat all wounds just by making packs available for wound treatment.

Our manual for treating wounds was designed to enable the staff to deal flexible with various situations, such as the use of a dressing trolley, the size of the infected wound, and the wound cleaning itself. In addition, the purpose was to design a manual to reduce medical costs and the chances of hospital staff contracting antiseptic-induced contact dermatitis or latex allergies, which could be implemented simply and effectively by all staff members. Educational courses concerning proper hand hygiene are still being debated,[9,10] but manuals supporting this technique are not being questioned.

Hand hygiene is recommended when treating each infected wound,[4,9,10] and cross-infection cannot be prevented simply by washing the hands after treatment. This is because even if hand hygiene is performed once an infected wound has been treated, the hands again come into contact with the patient's immediate surroundings and the bandaging utensils before the treating physician moves on to the next patient. As a consequence, the hands become contaminated and the infection may be carried to the next patient to be treated. In addition, even if proper hand hygiene is performed before treatment, the doctor or nurse's hands will come into contact with the patient's surroundings after they have been disinfected, thus resulting in hand contamination and cross-infection. That is why consideration must be given to the timing of hand hygiene. In addition, when the staff members' hands come into contact with the dressing trolley and so forth after disinfecting the hands, there is a risk that the hands will again become contaminated, and this contaminant from the dressing trolley will be carried to other patients being treated. It is therefore essential that the roles of the persons treating the wounds and other caregivers be separated into nonsterile and sterile tasks. This issue is also perceived differently among individual medical personnel. Some people stress strict hand hygiene, while others believe that brief hand washing is acceptable. Because there are different opinions within the medical setting, the effects of measures to combat cross-infection are not realized and educational efforts do not improve the overall environment, and hence the need has arisen for the present type of manual. The use of such a manual has not been looked into previously.

In the manual that we created, washing the hands was deemed unnecessary before entering a patient's room. Even if the hands are washed before entering the room of a patient, it is completely meaningless to do so because the dressing trolley still needs to be wheeled in, the curtains drawn, and the patient's environment entered into in order to reach the patient's bedside.

Next, it is effective for the medical staff to check all of the necessary equipment, move alongside the patient, and then wash their hands so that no pathogenic bacteria are transferred from other patients. In reality, our investigation also revealed that the hand bacterial count before hand hygiene before treatment reached 10^{3-7}. Most of the contaminated bacteria on the hands before treatment were passing bacteria and only mildly pathogenic. However, MRSA was isolated from two cases so the hands do indeed need to be washed before treatment.

Gloves should not be worn until after removing the gown of the patient awaiting treatment and exposing the dressing, but this is done primarily to prevent tape sticking to the gloves. By peeling off the tape directly with the fingers, damage to the surface of the patient's skin and contact dermatitis are prevented. However, since the old dressing contains infectious effusion, the wearing of gloves is required. Consequently, it is necessary to wear gloves from that point on, immediately after peeling the tape back, until the patient has been treated and the wound has been covered with a new dressing. It is important that all procedures involving the risk of the hands becoming contaminated from the dirty dressing or wound cleaning be done after treatment. When caregiving personnel perform such unhygienic procedures there is a risk that clean equipment on the dressing trolley will also become contaminated. The caregiving staff should therefore not perform any unhygienic procedures. Once the procedure on the wound has been completed and a treating staff member has covered the wound with a new dressing, then the caregiving staff member should apply tape to the new dressing. During this time, the treating staff should place any infectious waste in a plastic bag, which in turn should be placed in an infectious waste disposal container. The treating staff should then remove their gloves and disinfect their hands before moving on to the next patient. Before disinfecting their hands after treatment, 10^{3-5} cfu/hand bacteria were detected on the hands of the treating staff members. The fact that most were isolated bacteria such as MRSA from patient wounds highlights the extreme importance of washing the hands after treatment.

However, a comparison of the incidence rates of MRSA isolated from patients before and after this technique was adopted during the target period revealed a significant reduction in patients with isolated MRSA after the technique was applied, which reascertained the importance of hand hygiene as a measure against MRSA infections. In addition, based on the clinical PFGE typing of the MRSA isolates during the target period, the same type of MRSA was isolated before the introduction of the manual, whereas after the manual was enforced each isolate represented a different type of MRSA. This therefore shows that it is quite possible to prevent cross-infection via the hands of medical staff members when treating wounds.

In conclusion, while it is common knowledge that it is vitally important for the medical staff to wash their hands to prevent hospital infection, implementing this fully has been an extremely difficult problem. One of the reasons has been the difficulty of medical personnel agreeing on the timing of hand disinfection, the decision of which has been left to each individual. A manual such as ours detailing the present protocol can be shown to all medical personnel, who can then point out the faults of each other's technique. This would thus likely contribute to the education and awareness of the medical staff involved in infectious wound treatment. The bacteriological and clinical validity of the present manual has also been demonstrated.

References

1. Boyce JM, Pittet D. Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. Healthcare Infection Control Practices Advisory Committee. Society for Healthcare Epidemi-

ology of America. Association for Professionals in Infection Control. Infectious Diseases Society of America. Hand Hygiene Task Force. Infect Control Hosp Epidemiol 2002;23:S3–40.
2. Larson EL. APIC Guideline for hand washing and hand antisepsis in health-care settings. Am J Infect Control 1995;23:251–69.
3. Voss A, Widmer AF. No time for handwashing!? Handwashing versus alcoholic rub: can we afford 100% compliance? Infect Control Hosp Epidemiol 1997;18:205–8.
4. Olsen RJ, Lynch P, Coyle MB, Cummings J, Bokete T, Stamm WE. Examination gloves as barriers to band contamination in clinical practice. JAMA 1993;270:350–3.
5. Tenorio AR, Badri SM, Sahgal NB, Hota B, Matsushek M, Hayden MK, et al. Effectiveness of gloves in preventing personnel hand carriage of vancomycin-resistant enterococcus (VRE) after patient care. Clin Infect Dis 2001;32:826–9.
6. Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. Hospital Infection Control Practices Advisory Committee. Infect Control Hosp Epidemiol 1999;20:250–78.
7. Larson E, Friedman C, Cohran J, Treston-Aurand J, Green S. Prevalence and correlates of skin damage on the hand of nurses. Heart Lung 1996;26:404–12.
8. Kusachi S, Sumiyama Y, Nagao J, Kawai K, Arima Y, Yoshida Y, et al. New methods of control against postoperative methicillin-resistant *Staphylococcus aureus* infection. Surg Today 1999;29: 724–9.
9. Thunberg Sjostrom H, Skyman E, Hellstrom L, Kula M, Grinevika V. Cross-infection prevention, basic hygiene practices and education within nursing and health care in Latvia: a Swedish-Latvian practice development project. Nurse Educ Today 2003; 23:404–11.
10. Pittet D. Hand hygiene: improved standards and practice for hospital care. Curr Opin Infect Dis 2003;16:327–35.

Surg Today (2006) 36:107–113
DOI 10.1007/s00595-005-3112-6

SURGERY TODAY

Review Article

Questionnaire on Perioperative Antibiotic Therapy in 2003: Postoperative Prophylaxis

Yoshinobu Sumiyama, Shinya Kusachi, Yuichi Yoshida, Yoichi Arima, Hidenori Tanaka, Yoichi Nakamura, Jiro Nagao, Yoshihisa Saida, Manabu Watanabe, and Junko Sato

Third Department of Surgery, Toho University School of Medicine, 2-17-6 Ohashi, Meguro-ku, Tokyo 153-8515, Japan

Abstract
We distributed a questionnaire to institutions accredited by the Japan Surgical Society asking about the use of antibiotics in digestive tract surgery in Japan in 2003, and compared the results with those of a similar questionnaire distributed in 1993. The period of antibiotic administration for esophageal resection was at least 6 days in 64.9% of the 1993 questionnaire responses, but less than 4 days in 60.4% of the present questionnaire responses. For distal gastrectomy, antibiotics were given for 5 days postoperatively at 53.0% of the responding institutions in the 1993 survey, but for only 3 days, at 72.4%, in the present survey. An oral antibiotic was given as part of antibacterial colon preparation before colon resection at 70% or more of the institutions in the 1993 survey, while no antibiotic colon preparation was given at 80% of the institutions in the present survey. The period of antibiotic administration for laparoscopic cholecystectomy was at least 4 days in 72% of the institutions in the 1993 survey, but this decreased remarkably to fewer than 2 days at 80.8% of the institutions in the current survey. There were no differences in the selection of antibiotics between the two surveys. The period of antibiotic administration has decreased remarkably in the last decade.

Key words Postoperative infection · Prophylaxis · Surgical site infection · Antibiotics

Introduction

Both drug selection and the periods of administration of perioperative antibiotic therapy in Japan differ considerably from those in Western countries.[1–3] However, the protocols for postoperative antibiotic therapy in Japan were revised after the outbreak of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections in the late 1980s.[4] At the 43rd Conference of the Japanese Society of Gastroenterological Surgery in 1994, a panel discussion called "On the usage methods of antibiotic agents in gastroenterological surgery" published the results of a questionnaire on the use of antibiotics in gastroenterological surgery in 1993.[5] The Japanese Association for Infectious Disease and the Japanese Society for Chemotherapy published an Antibiotic Guide 10 years later. An observation of related societies' titles clearly confirms that the trends of perioperative antibiotic usage are changing.

Thus, we recently sent out a questionnaire survey targeting institutions accredited by the Japan Surgical Society, to establish the present status of perioperative antibiotic therapy. We also evaluated the changes in the last 10 years.

Methods

We asked the Chief Medical Officers of 771 institutions accredited by the Japan Surgical Society to respond to the issues listed below. The response format was sent by fax, clearly stating the name of the person in charge.

Results

We received responses from 550 of the 771 institutions targeted, resulting in a response rate of 71.3%.

Decision-Making About Perioperative Antibiotic Therapy

The answers about perioperative antibiotic therapy decision-making are given in Table 1. In the 1993 ques-

Reprint requests to: Y. Sumiyama
Received: September 3, 2004 / Accepted: March 15, 2005

tionnaire, 80.0% of the responding institutions left the decision to the physician in charge, but in he present questionnaire, 41.7% stated that the decision was incorporated into the group or clinical pathway, and only 55.8% of institutions left the decision to the physician. This suggests that control over the usage of antibiotics is being dispersed to different medical care teams or medical care units.

Start of Antibiotic Administration

The protocols for starting antibiotic administration on the day of surgery are given in Table 2. Of the institutions that administered antibiotics in the ward, the time antibiotics were started before surgery was "1 hour prior" in 51.7%, and "30 minutes prior" in 20.3%; thus, at least 70% started the administration of antibiotics 30 min to 1 h before surgery. In the 1993 questionnaire, only 19.3% of the responding institutions administered antibiotics to all patients during surgery, including immediately before and during surgery, but in the present questionnaire at least 70% did. This suggests that the Western trend of administering antibiotics, which until recently was followed randomly in Japan, has now been adopted without resistance since the introduction of Evidence-Based Medicine (EBM).

Thoracoesophageal Resection

In response to "What drugs (drug names) do you use as postoperative prophylactics for thoracic esophageal resection involving reconstruction accompanying esophageal resection with right thoracolaparotomy and 3 field lymph node dissection?", all surgeons reported using first- and second-generation cephems (Fig. 1). There were no major differences in the 1993 questionnaire regarding the selection of postoperative prophylactic antibiotics given in thoracic esophageal resection by right thoracolaparotomy. However, it is notable that in the 1993 questionnaire, the administration period was less than 4 days in only 3.8% of the responding institutions, 5 days in 31.8% of the responding institutions, and at least 6 days in 64.9% of the responding institutions, whereas in the present questionnaire the administration period had decreased to less than 4 days in 60.4% of the responding institutions (Table 3).

Table 1. Who selected perioperative antibiotics?

(a) Medical care unit or group	27.1%
(b) Integrated into clinical pathway	14.6%
(c) Physician in charge	55.8%
(d) Other	1.8%
(b + c)	0.6%
No answer	0.2%

Table 2. Start of antibiotic administration

(a) In the ward	21.5%
(b) Immediately before surgery	53.6%
(c) After the commencement of surgery	16.0%
(d) After the completion of surgery	8.4%
Other	0.4%
No answer	0.2%

Table 3. Duration of antibiotic administration in esophageal resection

(a) Day of surgery only	0.9%
(b) Until POD 1	1.8%
(c) Until POD 2	10.9%
(d) Until POD 3	31.5%
(e) Until POD 4	15.3%
(f) Until POD 5	22.2%
(g) Until POD 6	8.2%
(h) Until POD 7 or later	6.0%
Other	0.9%
No answer	2.4%

POD, postoperative day

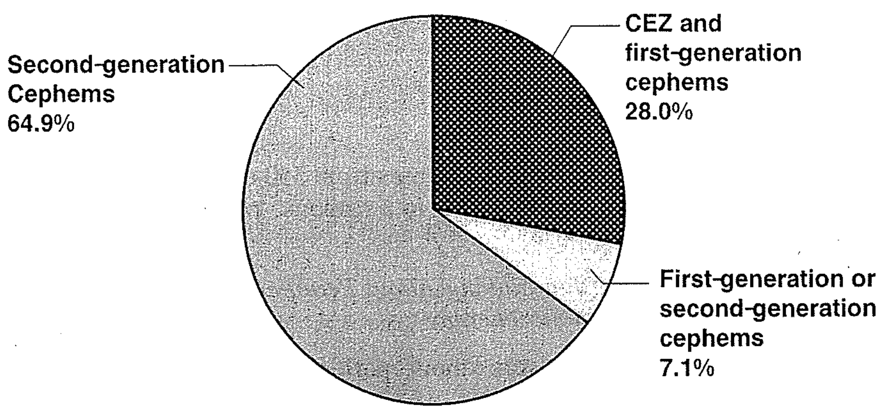

Fig. 1. Types of antibiotics given for thoracic esophageal resection via right thoracolaparotomy. Among the second-generation cephems, CTM, CMZ, and FMOX were used almost equally. First- and second-generation cephems accounted for 100%