行政院國家科學委員會專題研究計劃成果報告

計劃名稱：早期經腸營養法改善病人術後壓賀爾蒙與細胞激素反應
Early Enteral Nutrition Improves Stress Hormone and Cytokine Responses after General Surgery

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中文摘要

外科侵襲時，包括手術、外科感染、燒傷等等，會引發細胞激素與接著分子反應。適當的細胞激素分泌可提升病人免疫力與增進蛋白質代謝，加速病人的復元。但當這些細胞激素全身性過度反應(Systemic Exaggerated Response)時反而會傷害病人，造成多器官功能不全(Multiple Organ Failure)。局部(Local)與全身性(Systemic)細胞激素與接著分子之反應，在身體對抗外科手術壓力時，扮演之角色可能不同。然而這種周術期局部與全身反應並不清楚。並且，以前關於營養投與途徑對人體細胞激素影響的研究，主要是針對細菌類毒素的反應，而非對手術本身的反應。營養輸入途徑如何影響病人術後局部與全身的細胞激素反應，目前並不十分清楚。本研究乃針消化系外科手術病患，探討術前、術後的局部以及全身的細胞激素與接著分子反應，以及在術後 72 小時以內給予早期經腸營養或靜脈營養(PN)，並比較二者在局部及全身細胞激素與接著分子反應。本計畫針對大腸癌症手術病人，一方面探討週術期(Perioperative Period)局部與全身的細胞激素以及接著分子反應有何不同。另一方面，比較早期經腸組與經靜脈營養組的不同反應。以 ELISA 方法測定手術前、後第 1、3、7 日血中，以及術後引流液中的 IL-6，IL-8 的濃度。另外，測定細胞激素引發的接著分子(Adhesion Molecule)， 包括 ICAM-1，E-Selectin，L-Selectin 及 P-Selectin。本研究結果顯示手術本身可引發不同的局部與全身細胞激素以及接著分子反應，術後早期經腸道營養對手術病人有較佳的細胞激素與接著分子調節效果。

關鍵詞：手術，經腸道營養，細胞激素(Cytokine)，接著分子(Adhesion Molecule)

ABSTRACT

Surgery may result in defense mechanisms against stress in patients. Classical studies on mechanisms of such defense mechanisms in patients were focussed on neuroendocrine response. Recent studies revealed that cytokine network is deeply involved in the biological response to surgical stress. However, characteristics of cytokine and adhesion molecule dynamics in perioperative period were not well clarified. This study is aimed to demonstrate the dynamics of local and systemic cytokine and adhesion molecule responses to operation. Nutritional routes have been reported to modify cytokine response to sepsis. However, is is unknown whether nutritional routes may influence cytokine production and adhesion molecule reaction in patients after surgery. This study was also designed to investigate whether early enteral nutrition influences local and systemic cytokine and soluble adhesion molecule responses in patients following surgery. Patients with colorectal cancer receice total parenteral nutrition (PN group) or an early enteral nutrition (ENT group) after the operation. Patients in the PN group received only PN without any oral intake. Patients in the ENT group receive an enteral nutrition since within 72 hours after operation. Blood samples

were collected before operation. Furthermore, samples of blood and drain are collected on post-operative day 1 (POD1), POD3, and POD7. Levels of IL-6 and IL-8 in plasma and local drain samples are determined. Soluble adhesion molecules, including ICAM-1, P-Selectin, E-Selectin and L-Selectin are also determined. Dynamics of local and systemic cytokine and adhesion molecules was demonstrated from the study. Routes of nutritional supply may modulate production of local and systemic cytokines and adhesion molecules responses after operation. Early enteral nutrition might provide better regulation of cytokine response after surgery.

Keywords: Operation, Cytokine, Adhesion Molecule, Nutritional route, Enteral Nutrition, IL-6, IL-8, L-Selectin, E-Selectin, P-Selectin, ICAM-1.

BACKGROUND AND PURPOSE

Surgical insults, including operation itself, result in defense response in the patients. Previous researches on mechanisms about the defense mechanisms in patients against insult were focussed on neuroendocrine response[1-3]. In addition to such neuroendocrine response, recent studies revealed that cytokine network is deeply involved in the response to surgical stress[4-5]. Early homeostatic immune response to injury is characterized by the initiation of proinflammatory mediator cascade mobilizing the cellular and humoral immune mechanisms. Extended surgical injuries may result in a dysregulated hyperinflammatory response associated with a progress to multiple organ failure[6]. However, characteristics of cytokine and adhesion molecule dynamics in perioperative period were not well clarified. Furthermore, biological roles between local and systemic responses of cytokine and adhesion molecules may be different, but not well studied[7].

Recent evidence suggests that nutritional supply routes influence the production of endogenous mediators following surgical insult[8-9]. The precise mechanisms by which nutritional routes influence cytokine responses of following surgical insult, remain, however, to be elucidated[10-12]. IL-6 and IL-8 among various cytokines, play important roles in host responses[13-14]. Pathophysiological functions of IL-6 include the activation of B cells, natural killer cells, and T cells; and IL-8 is a powerful chemotactant in neutrophil trafficking[15-16]. However, exaggerated systemic cytokine responses may be harmful to the host[17-18]. Proinflammatory cytokine activate adhesion molecule expression on endothelial and immune cells in responsive to inflammation[13]. It is unknown whether nutritional routes modulate adhesion molecule response in stress.

This study was to compare, simultaneously, the local and systemic responses of cytokiens and adhesion molecules in patients receiving operations for colorectal cancers. Furthermore, this study is also designed to investigate whether early enteral nutrition influence local and systemic cytokine and adhesion molecule response.

PATIENTS AND METHODS

Subjects (Table-1)

18 patients with colorectal cancer who were admitted and received operation in National Taiwan University Hospital, and were grouped as a parenteral nutrition (PN) group and an ENT group. Patients in the PN group receive only PN without oral intake for more than 3 days after the operation. Patients in the ENT group started an enteral nutrition within 72 hours after the operation.

Local and Systemic Samples

Baseline laboratory samples are taken on admission and on post-operative day 7 (POD7). Blood samples are taken before the operation (Pre), and on POD1, POD3, and POD7.

Sample from the local drain tube are taken on POD1, POD3, and POD7.

Cytokine (IL-6, and IL-8) and adhesion molecules (ICAM-1, P-Selectin, L-Selectin, and E-Selectin) assay

Cytokines and adhesion molecules are measured using commercially available enzyme-linked immunosorbent assay (ELISA) methods (R&D Systems, Minneapolis, MN, USA). For each assay, a standard curve is constructed.

Stress Hormone Assay

Assay for stress hormone is still under investigation.

Data analysis

Data are expressed as means and standard error of the mean (SEM). Continuous data are analysis of variance (ANOVA) or the nonparametric testing method, based on the Mann-Whitney U test to compare means where appropriate. Fisher's exact test is used for the category data. The level of significance is considered to be $p<0.05$.

RESULTS

Local and systemic IL-6 dynamics (Fig-1)

IL-6 levels in the serum were lowest on Preop, and elevated significantly from Preop to POD1. The serum levels remain elevated until POD7, as compared with Preop. The serum IL-6 levels on POD1 were significantly higher than on POD3 and POD7.

IL-6 levels in the drain fluid were significantly higher than in the serum on either POD1, 3 and 7.

Local and systemic P-selectin dynamics (Fig-2)

The levels of P-selectin in the drain fluid decreased significantly from POD1 to POD7.

The levels of P-selectin elevated significantly from preop to POD1, and then diminished significantly from POD1 to POD3 and 7. The levels of P-selectin in the serum were significantly lower than in the drain fluid on either POD1, POD3, or POD7.

Local and systemic ICAM-1 (Fig-3) and E-Selectin (Fig-4) dynamics

The levels of ICAM-1 in the drain fluid elevated significantly from POD1 to POD3, and also from POD3 to POD7. The serum ICAM-1 diminished significantly from preop to POD1, and also the serum ICAM-1 levels diminished significantly from POD1 to PCD3. The levels of ICAM-1 in the drain fluid were significantly lower than in the serum on either POD1 and POD3. Serum and drain fluid E-Selectin dynamics exhibited an extremely similar pattern to ICAM-1.

Local and systemic L-Selectin (Fig-5) dynamics

Serum and drain fluid L-Selectin dynamics exhibited a similar pattern to ICAM-1.

Early enteral nutrition influenced cytokine and adhesion molecule response (Table-2)

ICAM-1 in the drain fluid in the ENT group on POD7 was significantly greater than in the PN group. By contrast, L-Selectin in the drain fluid in the ENT group was significantly greater than in the PN group.

SUMMARY

Perioperative local and systemic cytokine and adhesion molecule dynamics was clearly demonstrated from the present investigation. Local and systemic cytokine and adhesion molecule may be well regulated in patients receiving early enteral nutrition after surgery. Early Enteral nutrition is recommanded for patients after surgery if the patients are well tolerated.

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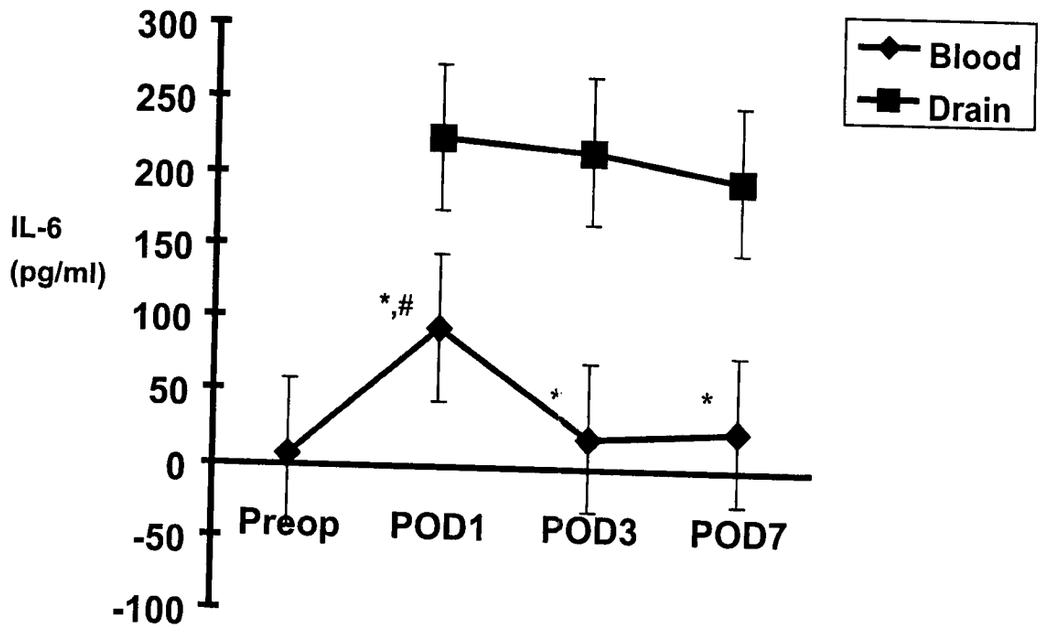
Table-1

Patient Characteristics		
Age (Yr)		63.4±9.1
Sex (F/M)		10±10
BH (cm)		158.1±6.8
BW (kg)		56.7±8.2
Rectal Ca. (LAR)		8
Colon Ca.		10
Op time (min)		184±68.3
Blood loss		373.1±291.9
Duke class	A	0
	B	7
	C	9
	D	2

Table-2

Group	ENT	PN	P
ICAM-1 (F) POD7	28.87±1.44	36.95±2.61	<0.05
L-Sel (F) POD3	6.94±0.63	4.95±0.37	<0.05

Fig-1



* : p<0.05 vs Perop
#: p<0.05 vs POD1

Fig-2

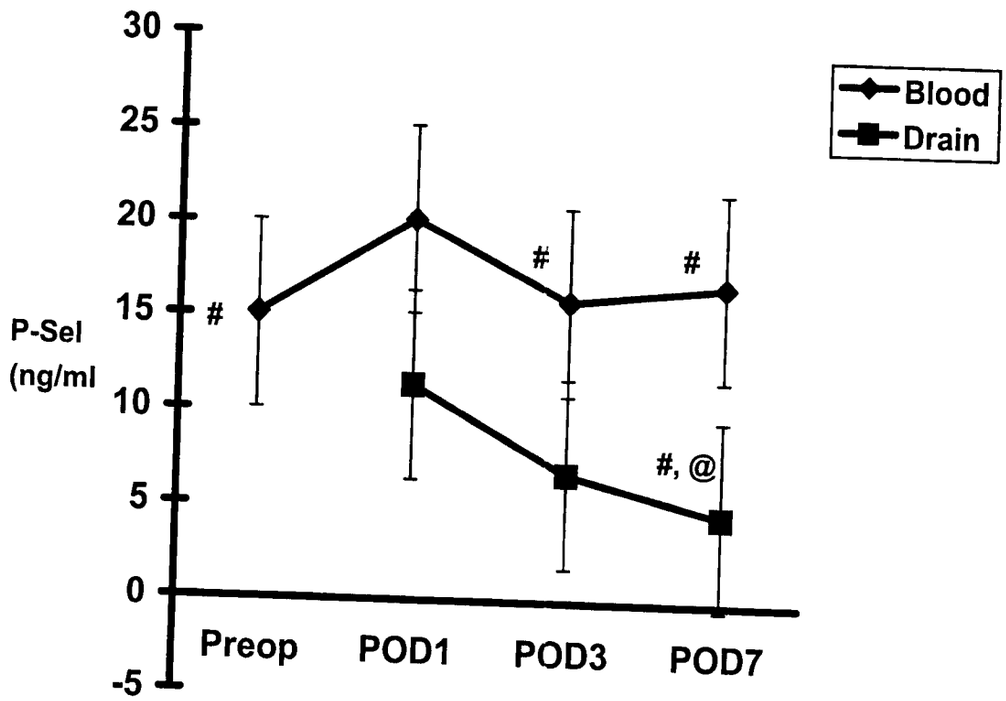
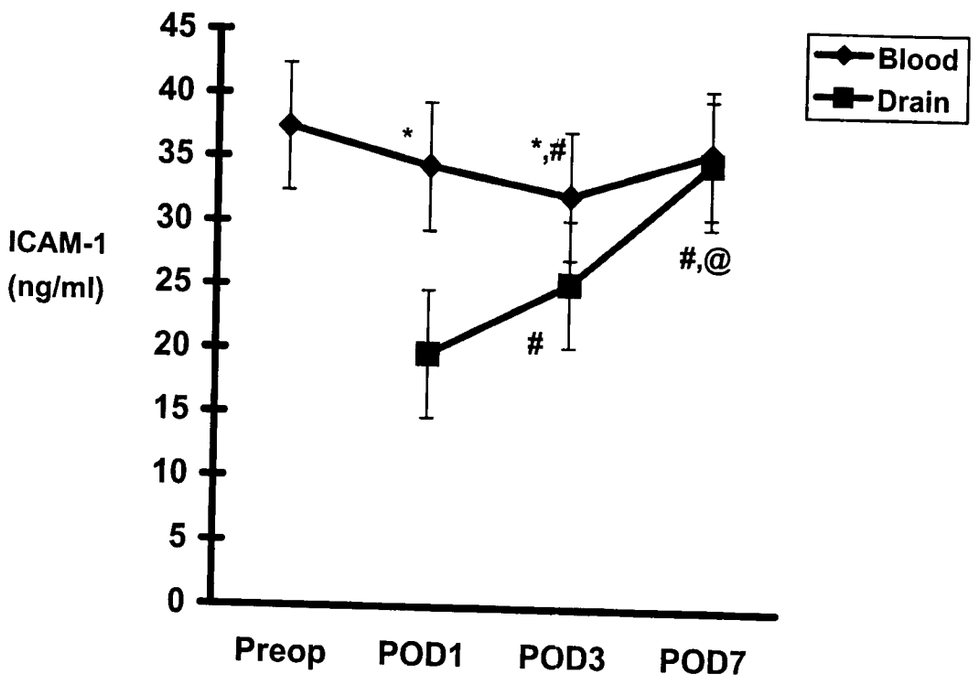

Preioperative P-Sel Dynamics
P-Sel (ng/ml
30
25
20
15
10
5
0
-5
Preop
POD1
POD3
POD7
Blood
Drain
#
#
#
#, @
#: p<0.05 vs POD1
@: p<0.05 vs POD3

Fig-3

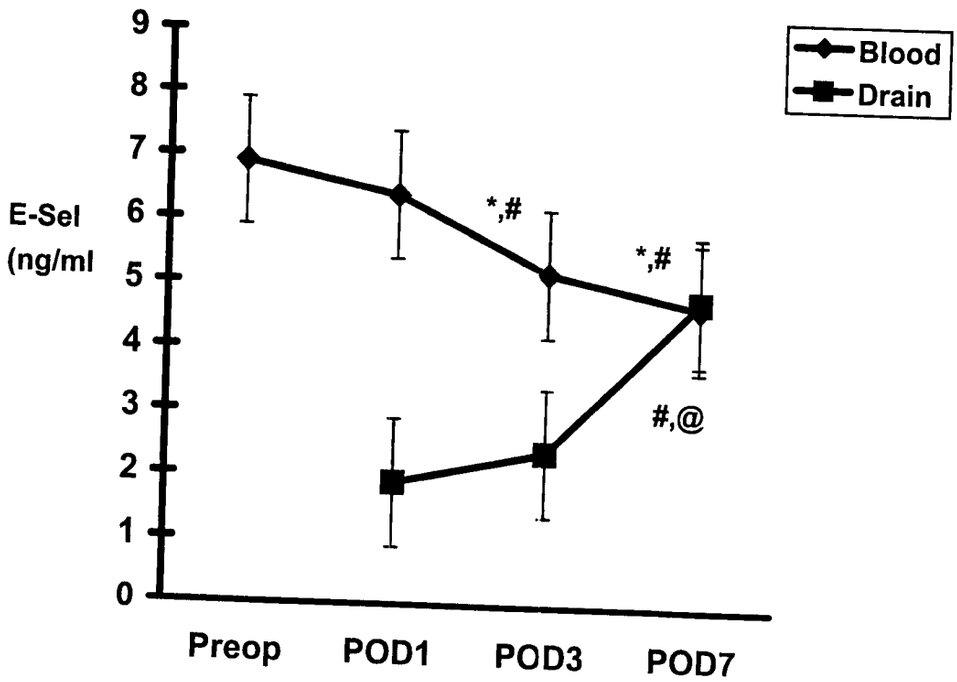
Perioperative ICAM-1 Dynamics



*: p<0.05 vs Perop
#: p<0.05 vs POD1
@: P<0.05 vs POD3

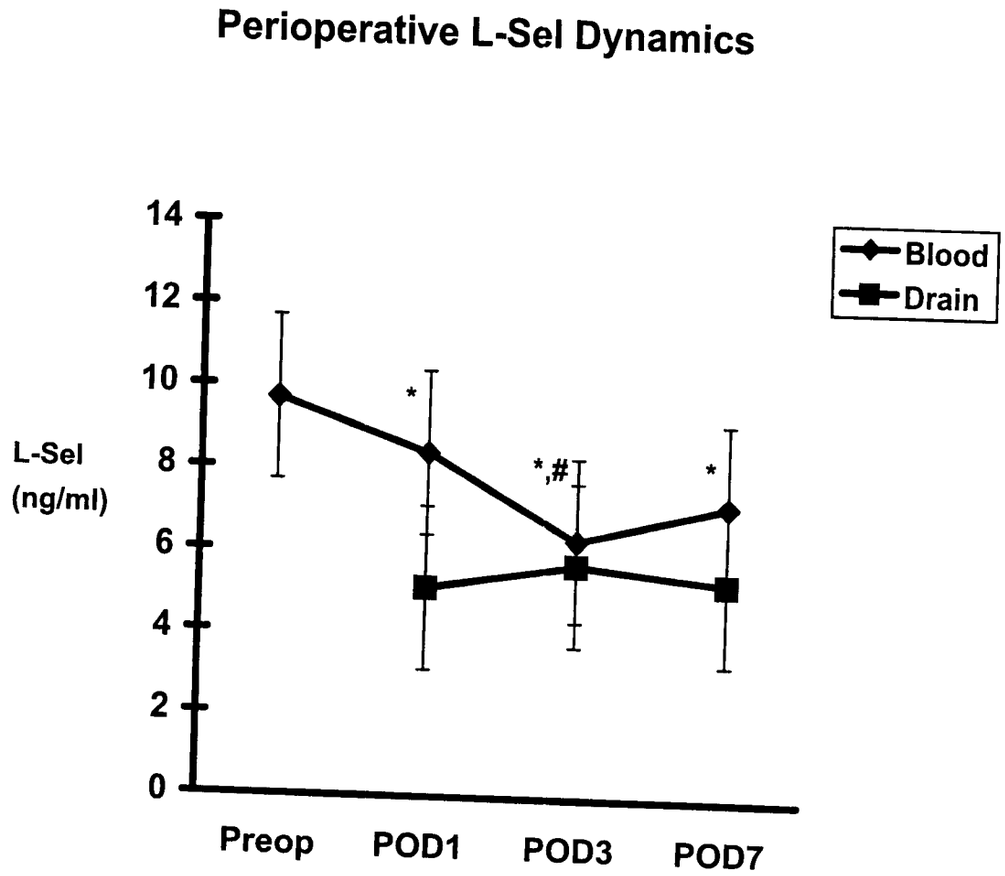
Fig-4

Perioperative E-Sel Dynamics



*: p<0.05 vs Preop
#: p<0.05 vs POD1
@: p<0.05 vs POD3

Fig-5


Perioperative L-Sel Dynamics
L-Sel
(ng/ml)
14
12
10
8
6
4
2
0
Preop
POD1
POD3
POD7
Blood
Drain
*
*,#
*
*: p<0.05 vs Preop
#: p<0.05 vs POD1