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計畫名稱: **胸腔手術後之細胞介質與黏滯因子之變化，及 FOY 對此變化及胸腔手術後臨床效果之評估**

The Change of Cytokines and Adhesion Molecules after Thoracic Surgery, and the Effect of Gabexate Mesylate（FOY）on this Change and the Clinical Implication

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一．中英文摘要:

關鍵字:重大手術，IL6，IL-8，ICAM-1

在胸腔手術中，食道摘除加上食道重建手術所引起的術後併發症與死亡率遠大於肺葉切除手術。本研究在探討食道摘除手術加上食道重建手術是否比肺葉切除手術引起更明顯的 IL-6，IL-8 與 ICAM-1 反應。方法:我們收集了 6 位食道癌手術與 10 位肺葉切除的病患，以 ELISA 測定其血中與胸腔引流液中的 IL-6．IL-8 與 ICAM-1。

結果:食道癌手術病患術後第一天其血中 IL6 明顯地升高，且其變化明顯大於肺葉切除手術。而第三天之後血中 ICAM-1 之升高也明顯大於肺葉切除手術。其差別在第五天更形明顯。而胸腔局部引流中 IL6 與 IL8 明顯高於血中 IL6 與 IL8。(約為血中 50-100)倍。

結論:食道手術比起肺葉摘除手術，在早期術後可引起較明顯的 IL-6 系統反應，在較晚期可引起較明顯的 ICAM-1 系統反應。二者(IL-6，ICAM-1)可為重大手術所造成的組織創傷提高一傷害性指標。

Abstract

Keywords: IL-6, IL-8, ICAM-1, Esophagectomy, Pulmonary Lobectomy.

Background: In thoracic surgery, esophagectomy combined with esophageal reconstruction has much higher postoperative morbidity and mortality than that of pulmonary lobectomy. IL-6 and IL-8 are important mediators, induced in response to a major trauma or surgery, and closely related to posttraumatic morbidity and mortality. ICAM-1 is the key regulator for the PMN associated cytotoxicity which is the common detrimental pathway for multiple organ failure (MOF). This study was conducted under the hypothesis that, compared to pulmonary lobectomy, esophgectomy combined with esophageal reconstruction surgery can induce more prominent local and systemic IL6, IL8 and ICAM-1 responses, which reflect the intensity of surgical trauma in thoracic surgery. ***Methods:*** The level of interleukin-6 (IL-6), interleukin-8 (IL-8) and soluble intercellular adhesion molecule-1 (sICAM-1) in the plasma and pleural drainage were serially examined in 6 patients receiving esophagectomy combined

with esophageal reconstruction and 10 with pulmonary lobectomy. ***Results:*** In the first postoperative day, patients receiving esophagectomy had significantly higher level of circulating IL6 than those with pulmonary lobectomy (782±391 vs 88±31[pg./ml], $p<0.05$) . The change of circulating IL8 was comparable between these two groups. The circulating sICAM-1 was significantly higher in esophagectomy group since the postoperative day 5, and the difference between the two groups expanded gradually with time. (774±89 vs 464±95, 845±82 vs 392±68[ng/ml], $p<0.05$ for postoperative days 5, and 7 respectively) The concentration of IL6 and IL8 in pleural drainage was 50 to 100 times higher than that in plasma. In contrast, the sICAM-1 level in plasma was similar to that of pleural drainage. In the postoperative days 3 and 5 the sICAM-1 level in pleural drainage was significantly correlated with that in plasma.(day 3: $p=0.019$, $R=0.57$; day 5: $p=0.049$, $R=0.51$) ***Conclusion:*** Esophgectomy with esophageal reconstruction surgery, compared to pulmonary lobectomy, can induce a more intensive systemic IL6 response in the early postoperative period and followed by a more obvious elevation of circulating sICAM-1 in the later period. This implies delay endothelial activation following transient cytokine stimulation after extensive surgical trauma by esophgectomy and the vulnerability to remote organ damage in the patients receiving esophgectomy.

二．計畫緣由與目的：

In the field of thoracic surgery, esophagectomy combined with esophageal reconstruction still remain a procedure with substantially high postoperative morbidity and mortality. The average hospital mortality of esophagectomy in a review of 130 papers from 1980 to 1988 was 13% (1), and even up to 19% in some series (2,3). In contrast, pulmonary lobectomy, even for lung cancer, seems to be a relatively safer procedure with hospital mortality around 2.9% (4). The pulmonary complication ending up with acute respiratory distress syndrome (ARDS) is the leading cause for perioperative mortality following esophagectomy(5). The neutrophilic leukocytes (PMN) induced tissue damage is the final common pathway in the pathogenesis of ARDS and multiple organ failure (MOF)(6). This process is facilitated via the interaction of various adhesion molecules expressed on the leukocytes and vascular endothelium(7). The intercellular adhesion molecule-1 (ICAM-1), expressed on the vascular

endothelium , is responsible for the late stage firm adhesion between PMN and endothelium, and the extravasation of PMN into the tissue(7-9). It is believed to be a pivotal regulator for PMN-mediated cytotoxicity(10).

Trauma produced by the surgical procedure is a very potent initiator for a lot of inflammatory cytokines such as TNF, IL-1, IL6, IL-8, and interferon-γ which in turn can promote expression of ICAM-1 on vascular endothelial cells, as well as β2 integrin (CD11b/CD18) on neutrophil (8,9,11). Among these cytokines, IL-6 was considered to be an integral mediator for the response under surgical injury or trauma(12). IL-8 was also an potent chemoattractants, activators of PMN and has a close association for the development of ARDS(13,14).

At the present time, it is not clear whether esophagectomy combined with esophageal reconstruction will produce more prominent cytokine responses and adhesion molecule shedding than pulmonary lobectomy . We therefore designed this study to evaluate these two groups of patients by serial examination of local and systemic IL-6 and IL-8 responses and shedding of sICAM-1.

三．結果與討論

Results

Clinical Profiles

Ten patients with pulmonary lobectomy and 6 patients with esophagectomy were enrolled in this study. Two patients received pulmonary lobectomy due to aspergilloma, one due to pulmonary tuberculosis, one due to bronchogenic cyst and 6 due to lung cancer. All of the patients underwent esophgectomy due to esophageal cancer. Two patients of the lobectomy group were females while all of the patients of esophageal cancer group were males. There was no difference in age, preoperative hemoglobin and albumin level and predictive postoperative FEV1 value. However the esophagectomy group have significantly more operation time and intraoperative blood loss than that of lobectomy group ($p< 0.001$). (Table 1) The patients undergoing lobectomy was extubated and resumed spontaneous breathing in the operative day or one day after operation. The patients with esophagectomy received mechanical ventilatory support at least for 3 days after operation and then gradually weaned

from mechanical ventilator. The weaning courses of all the patients with esophagectomy were also smooth.

Figure 1 and 2 illustrates the IL6 in blood and pleural drainage in both groups of patients respectively. Examining with MANOVA, both groups of lobectomy and esophagectomy had a significant change of IL-6 in the postoperative course both in blood and pleural effusion.($p<0.05$ for time effect) The IL6 level in blood increased remarkably in the postoperative course for both groups. The response in blood is different significantly between the two operative groups.($p<0.05$ between groups) In the first postoperative day, the esophagectomy group has a significant higher level of circulating IL6 than the lobectomy group.($p<0.01$) In contrast to the blood response, the IL6 level in the pleural drainage of the lobectomy group is highest in the first postoperative day and significantly higher than that of esophagectomy group.($p<0.01$) The IL-6 in pleural drainage decreased gradually and approximate the baseline level of zero in the fifth days.($p<0.05$ compared to POD1) The level of IL6 is much higher in pleural drainage than in blood by 30 to 1000 times in the first to three postoperative days.

As for IL8 in blood and pleural drainage which are shown in figure Figure 3 and 4 respectively, the change in the postoperative course for both groups is significant in the pleural drainage ($p<0.001$ for time effect) but not in the blood. There were no difference between the two groups for the IL8 response both in blood and pleural drainage. The IL8 level in pleural drainage has over 100 times higher than that in blood. The IL8 in pleural drainage rose progressively with time in contrast to that of IL6 in pleural drainage which decreased to baseline level in the 5th postoperative day. The IL-8 in 7th postoperative day in pleural drainage of the both surgical groups were significantly higher than that in first postoperative day.($p<0.05$)

Figure 5 and 6 depicts the sICAM-1 in blood and pleural effusion respectively. The

sICAM-1 of both groups in pleural effusion has a significant change in the postoperative course.($p<0.05$ for time effect) However, the difference between the two groups in pleural drainage was not significant. The sICAM-1 in blood also changed significantly in both groups after operation.($p<0.05$ for time effect) The changing scale in blood of both groups was significantly different as well. From the fifth postoperative day, the esophagectomy group has a higher level of circulating sICAM-1 than that in lobectomy group.($p<0.05$) The difference between groups was expanded in the following 7th days.($p<0.001$: for the interaction of groups and time in MANOVA) The level of sICAM-1 in blood and pleural drainage was similar, ranging between 200ng/ml to 800 ng/ml. In the postoperative days 3 and 5, the ICAM-1 in pleural drainage was significantly correlated with that of systemic sICAM-1 level (day 3: $p=0.019$, $R=0.57$; day 5: $p=0.049$, $R=0.51$).

There is no significant correlation between the APACHE II scores and the systemic level of IL-6, IL-8 and sICAM-1 of both groups of the patients(data not shown).

Discussion

Esophagectomy with restoration of gastrointestinal tract continuity involves three fields of operation, the chest, abdomen and neck which can cause more extensive tissue trauma than that of pulmonary lobectomy. Longer operation time and more blood transfusion was found in this group of patients. In this study, we demonstrated that esophagectomy combined with esophgeal reconstruction can induce a higher level of circulating IL-6 than pulmonary lobectomy on the first postoperative day. The IL-6 is the major integral mediator in the response of human body to surgical stress(12). The postoperative tentative surge of IL-6 has been reported to be an important factor for the vulnerability of patients to postoperative morbidity and mortality (19). The IL-6 can activate T cell or PMN resulting in acute phase response. The PMN cytotoxicity and sequestration in oragns can also be induced under the stimulation of IL-6, leading to the organ dysfunction (17,18).

For a more objective evaluation of stress response to surgical trauma it was important to exclude the influences of other factors such as infection, major anastamotic leakage etc. We

limited our studied patients among those who without major postoperative complications during the study. The lobectomy group included patients of both benign and malignant diseases in that lobectomy for both disease entities have by far lower incidence of postoperative morbidity and mortality than esophgectomy combined with esophgeal reconstruction surgery (1-4, 16). Although the operation time and blood loss in operation was higher in the esophagectomy group, we can not see a significant correlation between the amount of blood loss or operation time and the level of postoperative circulating IL-6 level(data not shown). This implies that the systemic IL-6 response is more dependent upon the surgical procedure itself than solely upon the operation time or the blood loss.

IL-8, released under the stimulation of IL-1, TNF or LPS, can acts as a potent chemoattractants, activators of PMN and a angiogenetic mediator to help wound healing (13,20). Although the IL-8 in bronchoalveolar lavage fluid was suggested as an indicator to subsequent development of ARDS in at-risk patients (21), our data showed that the thoracic surgery will not elicit exert a significant change of circulating IL-8 in both groups of patients, who had a smooth postoperative course.

Previous in vitro observation or animal study has shown that IL-6 can induce expression of immediate-early gene encoding ICAM-1 (22,23). In our study, the sICAM-1 didn't become significantly different between the two groups until the postoperative day 5. After the postoperative 5th day, the esophagectomy group had a progressive uprising of sICAM-1 in contrast to the pulmonary lobectomy group who still remained around the level of preoperative baseline. These data implies the inflammatory cascades induced by esophagectomy, i.e., IL-6 surge is induced in the early postoperative period which contribute to increase the systemic shedding of sICAM-1 in the latter postoperative periods. The relative minor procedure of pulmonary lobectomy, however, didn't cause a significant change of sICAM-1 in circulation.

The precise stimuli for IL-6 release after mechanical trauma are yet to be defined at the present time. In human, nearly every tissue is capable of expressing IL-6 (12). In the model of hemorrhagic shock of rat the IL-6 in portal blood is higher than the level of systemic blood indicating gut as an important source in rats with shock (24). Our data shows that

over 100 folds of IL-6 and IL-8 was contained in the local pleural drainage fluid as compared with serum both in esophagectomy and pulmonary lobectomy patients. This shows surgical manipulation can induce high local production for IL-8 and IL-6. However, we also observe that IL-6 local production in pulmonary lobectomy group was significantly higher than that of esophagectomy group in the first postoperative day. This contradictory results for the local and systemic IL-6 responses in both groups have emphasized that 1): esophagectomy alone can produce a less IL-6 local response than pulmonary lobectomy in pleura cavity ; 2) the simultaneous undertaking of different surgical procedures such as esophagectomy with esophageal reconstruction will have a synergistic effect to induce a more intensive systemic inflammatory response.

In contrast to IL-6 and IL-8, the level of sICAM-1 in pleural drainage is similar to that in circulation. In the postoperative days 3 and 5, the sICAM-1 level in pleural drainage was significantly correlated with that in plasma. This correlation implies that the local sICAM-1 in pleural drainage may be "spilled" from the systemic circulation rather than produced by the surgical wound.

The clinical implication for the delayed elevation of systemic sICAM-1 following esophagectomy is unclear. The sICAM-1 elevation can be found 132 hours after the injury, in patients of major trauma who subsequently developed multiple organ failure(MOF) (25). Open heart surgery with cardiopulmonary bypass also has persistent elevation of sICAM-1 immediately after operation (26). In canines receiving cardiopulmonary bypass, the ICAM-1 expression on vascular endothelium is upregulated after rewarming from bypass (27). Therefore the increasing shedding of sICAM-1 in circulation may come after the up-regulation of ICAM-1 expressed on the endothelium which has somehow been activated after esophagectomy. It is note worthy that all of our data was collected from patients with a smooth postoperative course. All of the circulating level of IL-6 and sICAM-1 didn’t significantly correlated with the APACHE II scores in both groups of patients. This implies that the postoperative hypercytokinemia and increased shedding of sICAM-1 can just exert a subclinical effect in human and more mechanisms were need to eventually lead to perioperative morbidity and mortality. The theory of ‘second attack’ has been proposed for

the injury by a major operation that the transient hypercytokinemia in human can ‘prime’ the neutrophil to accummulate in vital organ but won’t result in organ dysfunction directly. It is the second episode of hypercytokinemia, caused by subsequent shock, sepsis or hypoxia etc, that will activate the neutrophil to attack the organs and lead to organ dysfunction(11). The delay shedding of sICAM-1 after esophagectomy with esophageal restoration surgery is for the first time demonstrated in this study. It deserves a lot of concern in clinical practice since that the increased systemic shedding of sICAM-1 may indicate the systemic activation of endothelium. More delicate care must be paid to these patients whose organs have more susceptibility to the attack of neutrophils.

It is concluded that esophagectomy with esophageal reconstruction surgery can induce a more obvious systemic IL-6 response than pulmonary lobectomy in the first postoperative day and more systemic shedding of sICAM-1 since postoperative day 5. The difference in the IL-6 and ICAM-1 systemic responses can serve as markers to reflect the different grades of surgical trauma between esophagectomy and pulmonary lobectomy. The delayed sICAM-1 elevation after esophagectomy may be a secondary response to the early postoperative surge of IL-6 which up-regulates the expression and promotes the shedding of sICAM-1 on the vascular endothelium. One must pay more attention to patients after esophgectomy once who has gone through the state of hypercytokinemia and endothelial activation. Anticytokine or anti-adhesion molecule therapy may be encouraged for the prevention of postoperative morbidity and mortality after this procedure.

五．計畫成果自評：

本研究可為重大手術提供一有價值的組織傷害指標，為日後併發症的預防與治療提供了重要的依據。惟其病患數目不多。需要大規模的研究以確定其意義。

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Table 1. Clinical characteristics of patients with lobectomy and esophagectomy

Patient Variables	Lobectomy(SE) (n=10)	Esophagectomy(SE) (n=6)	p
Age	54.8(20.6)	67.6(6.7)	NS
Albumin(gm/l)	4.0(0.5)	3.7(0.5)	NS
Hemoglobin(gm/l)	12.9(2.3)	12.5(1.7)	NS
Post OP Predicted FEV1(%)	83.5(23.3)	87.9(15.6)	NS
Operation Time(Hour)	5.9(4.9)	10.0(2.5)	<0.001
Operation Blood Loss(ml)	277(193)	616(394)	<0.001

NS: not significant SE: standard error

Fig.1
IL-6 in Blood

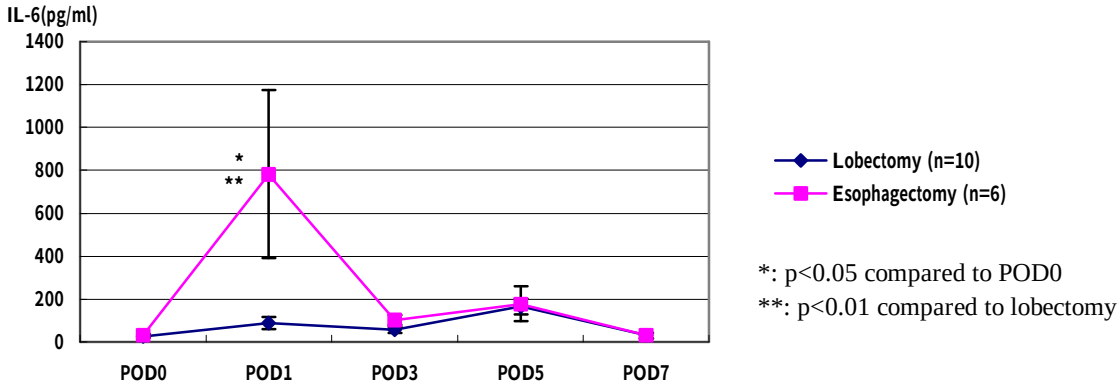

Fig.2
IL-6 in Pleural Drainage

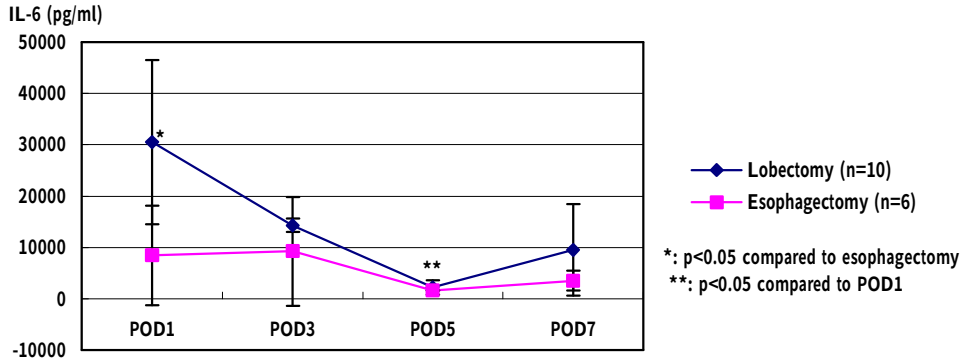

Fig.3
IL-8 in Blood

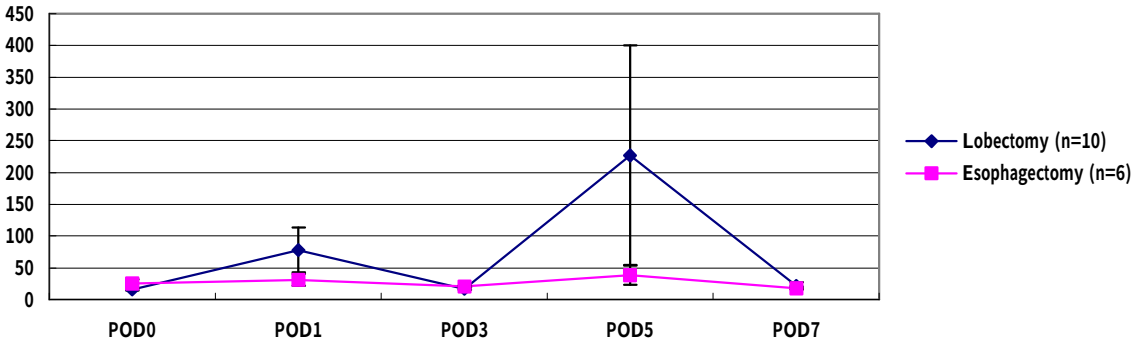

Fig.4
IL-8 in Pleural Drainage

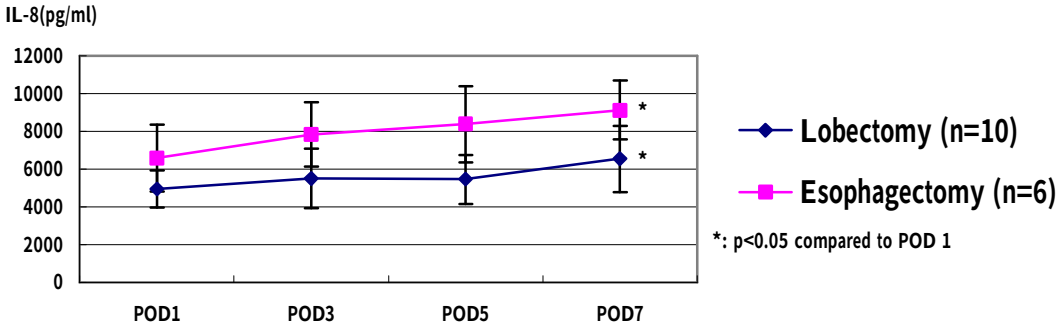

Fig.5
ICAM-1 in Blood

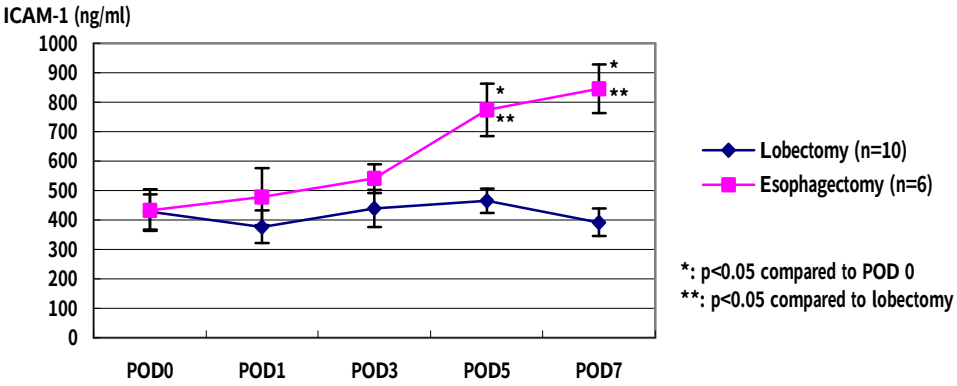

Fig.6
ICAM-1 in Pleural Drainage