行政院國家科學委員會補助專題研究計畫成果報告

胃癌手術 IL-6 反應及對胃癌細胞凋亡影響

IL-6 Response in Gastric Cancer Surgery and Its Effect on Apoptosis

計畫類別：☑個別型計畫　　□整合型計畫
計畫編號：NSC89－2314－B－002－434
執行期間：89 年 08 月 01 日至 90 年 07 月 31 日

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本成果報告包括以下應繳交之附件：
- □赴國外出差或研習心得報告一份
- □赴大陸地區出差或研習心得報告一份
- □出席國際學術會議心得報告及發表之論文各一份
- □國際合作研究計畫國外研究報告書一份

執行單位：**台大醫院　外科**

中　華　民　國　90　年　12月　03　日

結果：

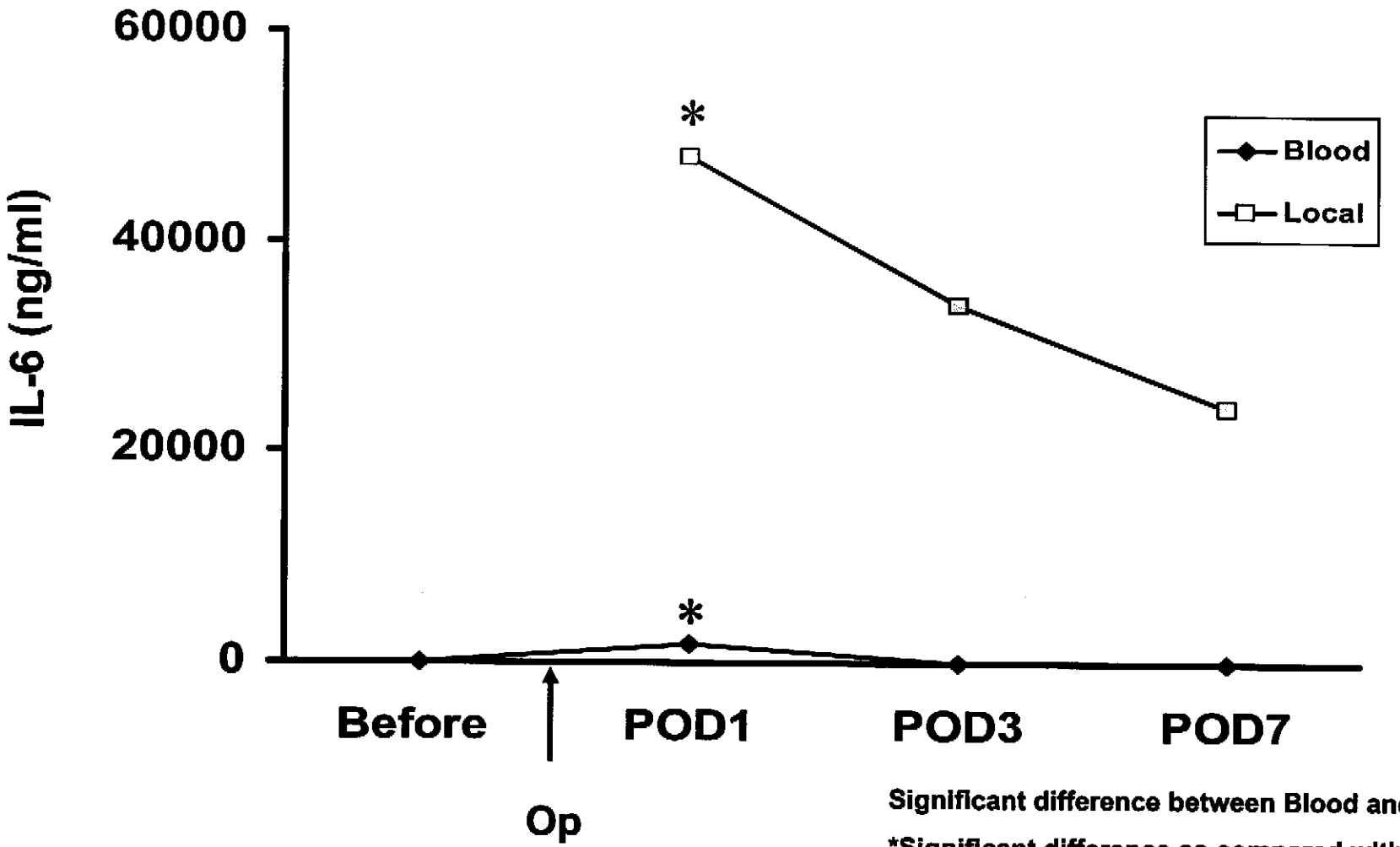
1. In vivo patient study
   (1) Fig-1. Local and Systemic IL-6 Response to Gastric Cancer Surgery
   (2) Fig-2. Local and Systemic ICAM-1 Response to Gastric Cancer Surgery
   (3) Fig-3. Local and Systemic E-sel Response to Gastric Cancer Surgery
   (4) Fig-4. Local and Systemic L-sel Response to Gastric Cancer Surgery

2. In vitro study

Apoptosis play a critical role in maintaining genomic integrity by selectively removing the most heavily damaged cells from the population. Reactive oxygen species (ROS) and certain inflammatory cytokines are always elevated during the human carcinogenic process. However, the biological significance of the interplay between ROS and inflammatory cytokine remains elusive. This study demonstrated that interleukin-6 (IL-6) effectively protects gastric cancer cells from the apoptosis induced by hydrogen peroxide (H_2O_2). The cell death signaling JNK pathway elicited by H_2O_2 is also inhibited by IL-6. We further found that Mcl-1, but not other Bcl-2 family members, was up-regulated by IL-6, by a substantial level over 24 h. We further transfected a *mcl-1*-overexpression vector, pCMV-*mcl-1*, into the AGS cells, and successfully obtained several *mcl-1*-overexpressing clones. Flow cytometric analysis shows that these *mcl-1*-overexpressed AGS cells are more resistant to the apoptosis induced by H_2O_2 when compared with the *neo* control AGS cells. Consistently, the activation of the JNK pathway induced by H_2O_2 is also blocked in *mcl-1*-overexpressed cells. These results indicate that the anti-apoptosis effect of IL-6 is, at least in part, due to the up-regulation of *mcl-1*. To our surprise, either IL-6 exposure or *mcl-1* overexpression fails to reduce the level of intracellualr peroxides in the AGS cells triggered by H_2O_2. This study also determined the level of 8-hydroxydeoxy-guanosine (8-OH-dGua), an indicator for oxidative DNA lesions in IL-6-treated or mcl-1-overexpressed AGS cells after treatment with H_2O_2. Notably, our results indicate that a majority of the 8-OH-dGua is efficiently removed in the AGS cells without IL-6 treatment, whereas only about 50% of the 8-OH-dGua was repaired in the IL-6-treated AGS cells after 24 h. Similarly, about 60-70% of the 8-OH-dGua also failed to repair and was retained in the genomic DNA of the *mcl-1* transfectants. Results in this study provide a novel mechanism by which up-regulation of the Mcl-1 protein by IL-6 may enhance the susceptibility to H_2O_2–induced oxidative DNA lesions by overriding apoptosis.

*此篇文章已被接受刊登在 Carcinogenesis 雜誌上。

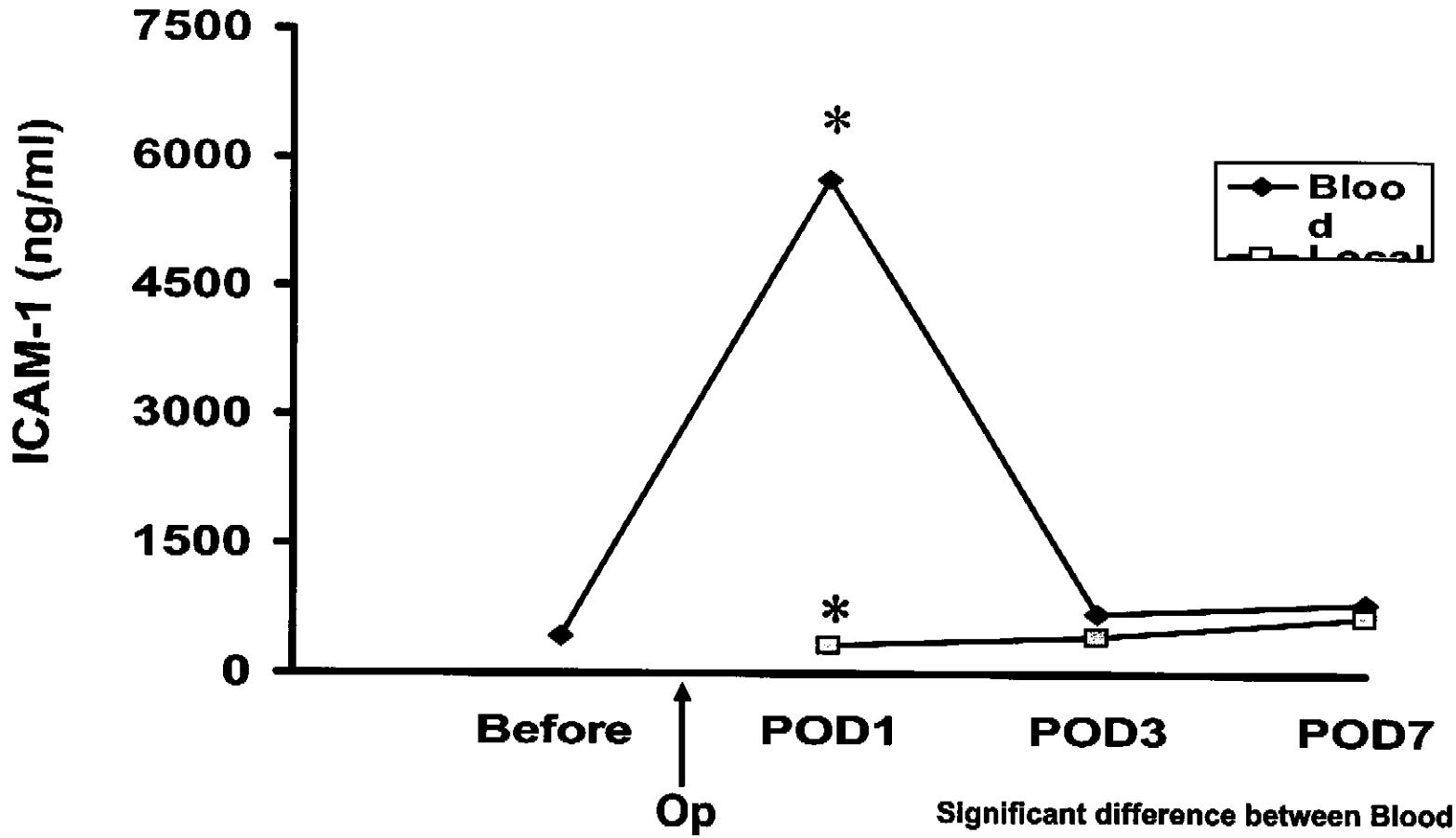
Fig-1. Local and Systemic IL-6 Response to Gastric Cancer Surgery



Significant difference between Blood and Local

*Significant difference as compared with other op day

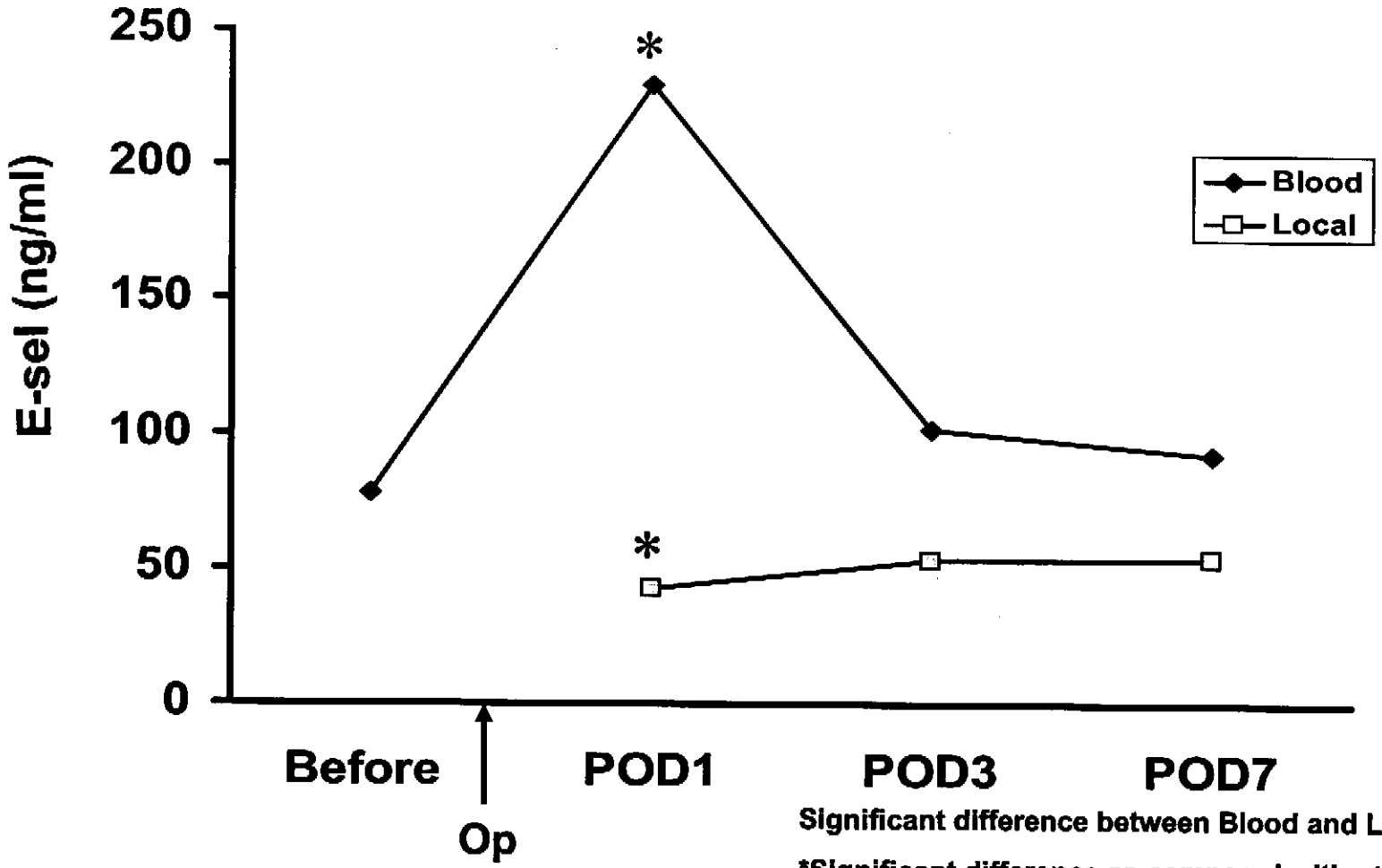
Fig-2. Local and Systemic ICAM-1 Response to Gastric Cancer Surgery



Significant difference between Blood and Local

*Significant difference as compared with other op day

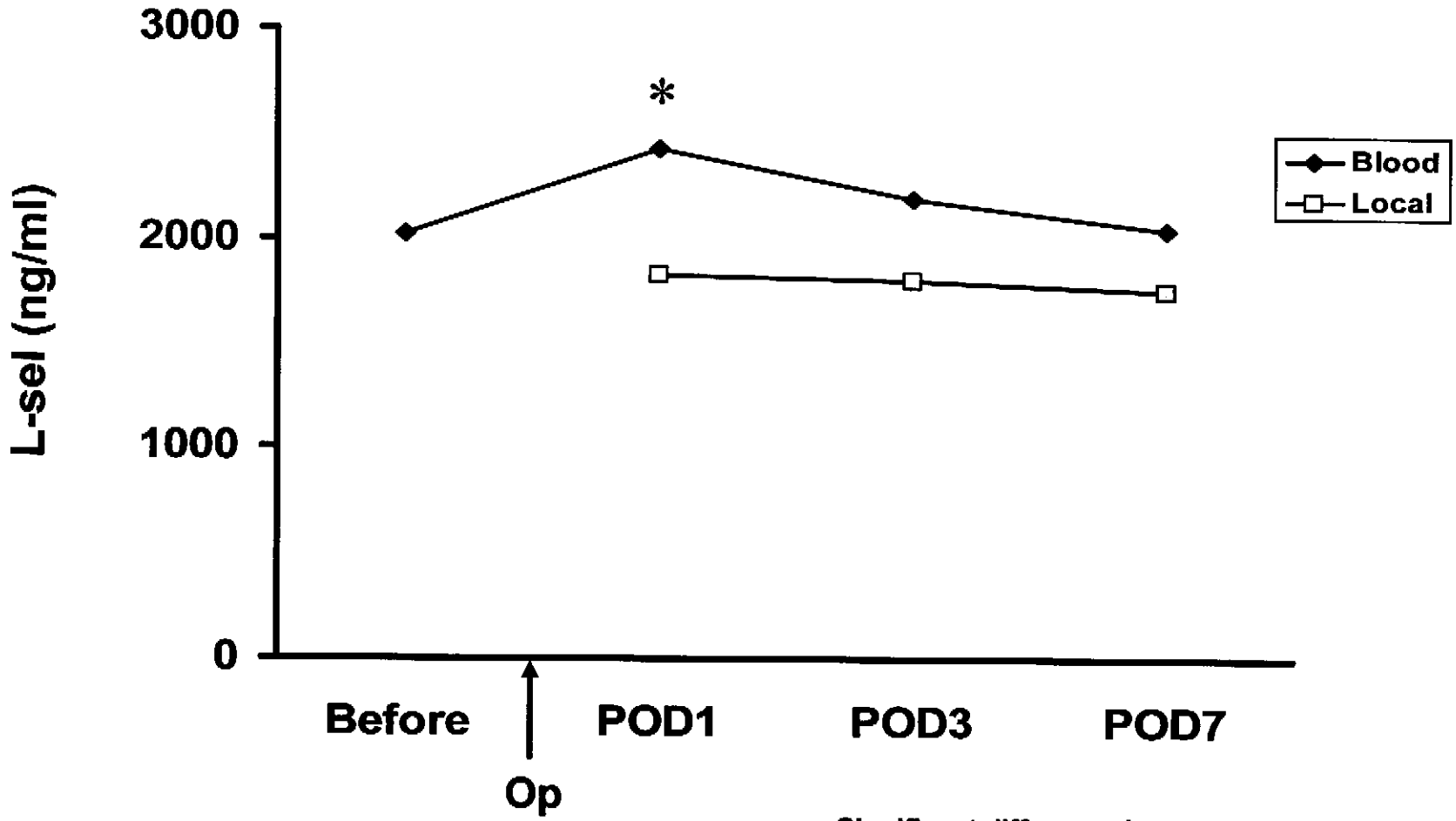
Fig-3. Local and Systemic E-sel Response to Gastric Cancer Surgery



Significant difference between Blood and Local

*Significant difference as compared with other op day

Fig-4. Local and Systemic L-sel Response to Gastric Cancer Surgery



Significant difference between Blood and Local

*Significant difference as compared with other op day