The Effect of Octreotide on Portal Vein and Peritoneal Fluid Cytokine Levels in Postoperative Adhesion Prevention

DENEYSEL AMELİYAT SONRASI KARINİÇİ YAPIŞIKLIK MODELİNDE OKTREOTİDİN PORTAL VEN VE PERİTON SIVISI SİTOKİN DÜZEYLERİNE ETKİSİ

Ömer GÜNAL, MD,[a] Mustafa DENİZ,[b] Arif ASLANER, MD,[a] Salah GHADOURI, MD[b]

[a]Department of General Surgery, Abant İzzet Baysal University, Düzce School of Medicine, DÜZCE
[b]Department of Physiology, Marmara University School of Medicine, İSTANBUL

Abstract

Objective: The aim of this study is to investigate the effect of octreotide on portal vein and peritoneal fluid TNF-α and IL-6 levels in the postoperative adhesion formation.

Material and Methods: Following an "adhesion model operation", 10 rats were given octreotide subcutaneously (25 μg/kg/day) for 10 days (study group) while other 10 rats did not receive any treatment (control group). Ten rats had only a midline laparotomy as sham. Adhesion scores, portal vein and peritoneal fluid cytokine levels were determined on the postoperative 10th day.

Results: Octreotide significantly reduced the total adhesion score. It has also reduced the portal vein IL-6 and TNF-α (147 ± 2 pg/mL; 146.7 ± 2.6 pg/mL respectively) levels as compared to those of control group (193.5 ± 10 pg/mL; 195.8 ± 11.2 pg/mL respectively). There was no reduction (IL-6 132; 143 and TNF-α 132.8; 143.7) on contrary, elevations in peritoneal fluid cytokine levels, comparing to control.

Conclusion: Octreotide reduces postoperative intraabdominal adhesion formation through the mechanisms those mediated by intestinal rather than peritoneal cytokine production.

Key Words: Adhesion, cytokine, octreotide

Özet

Amaç: Bu çalışmanın amacı, oktreotidin postoperatif yapışıklık oluşumunda portal ven ve periton sıvısındaki TNF-α ve IL-6 seviyelerine etkisini araştırmaktır.

Gereç ve Yöntemler: Standart bir "adhezyon model operasyonu"nu takiben 10 adet erişkin sıçana 10 gün süreyle subkutan yolla oktreotid (25 μg/kg/gün) uygulanırken (çalışma grubu) diğer 10 sıçana herhangi bir tedavi verilmedi (kontrol grubu). On sıçana sham operasyonu olarak sadece orta hat laparotomisi uygulandı. Postoperatif 10. gün adhezyon skorları, portal ven ve periton sıvısındaki sitokin seviyeleri değerlendirildi.

Bulgular: Oktreotid total adezyon skorunu belirgin olarak azalttı. Ayrıca portal ven IL-6 (147 ± 2 pg/mL) ve TNF-α (146.7 ± 2.6 pg/mL) seviyelerini kontrol grubundakine (IL-6= 193.5 ± 10 pg/mL; TNF-α= 195.8 ± 11.2 pg/mL) göre azalttığı izlendi. Peritoneal sitokin düzeylerinde azalma olmayıp, tersine, kontrol grubuna kıyasla yükselme izlendi (IL-6 132; 143 ve TNF-α 132.8; 143.7).

Sonuç: Oktreotid amliyat sonrası karıniçi yapışıklık oluşumunu peritonealden çok intestinal sitokin üretiminin yönlendirdiği mekanizmaları etkileyerek azaltmaktadır.

Anahtar Kelimeler: Adezyon, sitokin, oktreotid

Turkiye Klinikleri J Med Sci 2006, 26:252-257

Postoperative intraabdominal adhesions are common sequelae of abdominal operations and lead to numerous complications including pain, small bowel obstruction, difficult reoperations and infertility.[1,2] A great deal of efforts have been dedicated to reduce adhesion formation because of morbidity associated with adhesions. Despite these efforts, an ideal therapy or drug remains to be identified. Intraabdominal adhesion formation is a kind of aberrant wound healing process, which is working through some surrogate markers such as TNF-α and IL-6. TNF-α and IL-6 are mainly the products of activated macrophages.[3] They may also be released from the mesothelial cells of the peritoneum as a response to trauma.[4-7] Either of mesothelial cell or white blood cell origin, cytokine release to the peritoneal cavity and systemic circulation is inevitable after surgery. Intraperitoneal adhesion formation follows the sequence of tissue inflammation, fibrin deposition,

Geliş Tarihi/*Received:* 01.07.2004 **Kabul Tarihi/*Accepted:*** 31.10.2005

Yazışma Adresi/*Correspondence:* Ömer GÜNAL, MD
Abant İzzet Baysal University
Department of General Surgery, DÜZCE
gunal@ibu.edu.tr

fibrin organization, collagen formation and maturation with formation of adhesion.[8,9] Intraperitoneal adhesion formation begins with an inflammatory reaction that can be interfered with drugs that have antiinflammatory activity such as octreotide.[10-13]

Octreotide is an analogue of somatostatin, with the same biologic effects but a longer half-life. In clinical practice, it is generally used for its inhibitory effects on gastrointestinal peptides.[14,15] This study was designed to investigate the effect of octreotide on postoperative adhesion formation and the cytokine levels of body fluids.

Material and Methods

Thirty 200-250 gr male, 12 months old Wistar-albino rats were divided into 3 groups. All rats lived at room temperature (27°C) and were fed by standard pellet diet and tap water. Rats were fasted before surgery and were allowed to feed orally 12 hours after surgery. This study was approved by the Animal Ethics Committee of Düzce Medical School.

Adhesion model operation: Rats were anesthetized with ether (Ether hydrochloride-Plantafarma-Düzce) inhalation. Induction of anesthesia was accomplished by keeping the rats in a glass chamber that contained a 10 mL ether absorbed pad on the floor. General anesthesia was maintained by ether inhalation through a mask containing an ether-absorbed pad. All groups underwent a standard midline laparotomy under sterile conditions. Both sides of the caecum were scraped with a fine sandpaper until the muscular layer appeared with a gentle handling. A 1 x 1 cm peritoneal patch excision from the right anterior abdominal wall opposing to the caecal abrasion site was performed. Abdomen was closed with 3.0 silk sutures en-bloc, continuously. On the tenth day, all rats had the second-look laparotomy for adhesion scoring and portal vein and peritoneal fluid samplings.

Sham group (n= 10) underwent a midline laparotomy only without any treatment. Control group (n= 10) had adhesion model operation and did not receive treatment. Octreotide group (n= 10) received a somatostatin analog octreotide 25 μg/kg (Sandostatin, Novartis Corp, İstanbul) once a day, subcutaneously for seven days, after adhesion model operation.

Sampling and assays: At second look laparotomy, immediately after the adhesion evaluation, 1 mL of blood was withdrawn from the portal vein. Two mililiters of saline was injected to the peritoneal cavity, was stirred and withdrawn with a syringe. All samples were then kept at -70°C until they were assayed. IL-6 and TNF-α levels of portal vein and peritoneal fluid were measured using commercially available ELISA kits (CYTELISA-Cytimmune Sciences inc. Maryland, USA). The limits of the sensitivity of the assays were 16.8 pg/mL and 18.2 pg/mL for IL-6 and TNF-α, respectively.

Adhesion scoring: The extent and strength of the fibrous bands at the peritoneal defect site were recorded. As previously defined, adhesion scores were determined according to the criteria shown in Table 1, with respect to the strength (severity) and extension of adhesions.[16,17] Total adhesion score (TAS) was calculated by adding the mean of these two scores in each group.

Statistical analysis

All values were presented as mean ± standard error of mean. Adhesion scores were compared between control and octreotide groups with Mann-Whitney U test. Cytokine levels in portal vein

Table 1. Criteria for calculating the total adhesion score.

Scores	Severity	Extension
0	No adhesions	No adhesions
1	Mild, easily dissectable adhesions	Adhesions on 25% of the traumatized area (by 2.5 mm)
2	Moderate adhesions, nondissectable, did not tear the organ	Adhesions on 26% to 50% of the traumatized area (between 2.6-5 mm)
3	Dense adhesions, non-dissectable, tore organ when removed	Adhesions on 51% to 100% of the traumatized area (between 6-10 mm)

blood and peritoneal fluid were compared by the Wilcoxon Signed Rank test. Difference between the three groups was analyzed with Kruskal Wallis test. A p value of < 0.05 was considered statistically significant.

Results

TAS was reduced in the octreotide group (n= 10) when compared to the control (n= 10) group (p= 0.053 not quite significant, U'= 9.00). Despite a significant reduction in adhesion extension (p= 0.0175, U'= 6.5), an equivocal alleviation in adhesion severity score could not be obtained in octreotide group (n= 10) (p= 0.1649, U'= 13.5) (Table 2).

Portal vein IL-6 (Table 3) and TNF-α (Table 4) levels were higher than the peritoneal fluid IL-6 and TNF-α levels in the control (n= 10) and sham (n= 10) groups. Portal vein IL-6 (p= 0.2188) and TNF-α and peritoneal fluid (p= 0.9999) levels were similar in the octreotide (n= 10) group (Table 3, 4).

The difference in IL-6 and TNF-α levels between the 3 groups was not statistically significant (Kruskal-Wallis test; p= 1 for IL-6 and p= 1 for TNF-α). Increased peritoneal fluid IL-6 and TNF-α levels (Table 3 and 4) in the control (n= 10) group did not decrease with octreotide administration. However, significantly increased portal vein IL-6 and TNF-α levels in the control group displayed a considerable decrease in the octreotide group.

Table 2. Adhesion scores obtained in the experimental groups. p; comparison of sham with control. p*; comparison of octreotide with control.

Adhesion type	Control	Octreotide	p
Extension	2.4 (0.3)	1.2 (0.2)	0.0175
Severity	2.4 (0.4)	1.7 (0.3)	0.1649
Total Adhesion Scores	4.8 (0.6)	3 (0.4)	0.053

Table 3. Portal vein and peritoneal fluid IL-6 levels in different groups. p*; p value of Kruskal-Wallis analysis between the three groups. p; p value of Wilcoxon Signed Rank test between peritoneal fluid and portal vein blood levels. Values in paranthesis are s.e.m. values.

IL-6 (pg/mL)	Portal vein blood	Peritoneal fluid	p
Sham	149.7 (10)	123 (8)	0.0156
Control	193.5 (10)	132 (12)	0.0156
Octreotide	147 (2)	143 (3)	0.2188
p*	1	1	

Table 4. Portal vein and peritoneal fluid TNF-α levels at different groups. p*; Kruskal-Wallis analysis among the three groups. p; Wilcoxon Signed Rank test between peritoneal fluid and portal vein blood levels. Values in paranthesis are s.e.m. values.

TNF-α (pg/mL)	Portal vein blood	Peritoneal fluid	p
Sham	165.4 (8.3)	127.5 (7.2)	0.0156
Control	195.8 (11.2)	132.8 (12)	0.0313
Octreotide	146.7 (2.6)	146.7 (2.4)	0.9999
p*	1	1	

Discussion

The incidence of intraperitoneal adhesions ranges from 63 to 93 percent after general surgical abdominal operations and up to 97 percent after open gynecologic pelvic procedures.[1,2,18] Abdominal adhesions account for 54-74% of small bowel obstructions.[18] Approximately 80-90% of abdominal adhesions are due to surgical interventions, 5-20% arise from inflammatory causes and only 2-5% are congenital.[19] An understanding of the adhesion formation pathophysiology helps us to define new methods of adhesion prevention.

Studies report that neutrophils take place in the granulation tissue that grows during the first three days of the peritoneal injury.[20] Alatas showed that octreotide decreased the peritoneal adhesion score.[21] In the same study, peritoneal tissue myeloperoxidase level-a marker of polymorphonuclear infiltration-also decreased. Lai demonstrated that octreotide reduced the incidence of postoperative intraperitoneal adhesions in rats.[22] In addition, Baykal and collegues suggested that octreotide had a beneficial effect in decreasing postoperative adhesion formation evaluated by scoring of adhe-

sions.[23] Our results are in concordance with these two studies. In the former study, a single intraperitoneal dose of 120-150 μg/kg per rat or a concurrent intramuscular dose of 20 μg/kg for 14 days were administered.[22] However, the latter study detected that much smaller doses such as a single intraperitoneal dose of 10 μg/kg was adequate for adhesion prevention. We used a subcutaneous dose of 25 μg/kg/day for 10 days. This dose was adequate to reduce the TAS from 4.8 to 3 in our study. There are several mechanisms to explain the effect of octreotide in decreasing postoperative adhesion formation. Angiopeptin, a somatostatin analogue, decreases epidermal growth factor levels, insuline like growth factor-1 and platelet derived growth factor.[24,25] Octretide also inhibits angiogenesis.[26]

Injury to the peritoneum leads to formation of fibrinous exudate.[10] Adhesion formation starts with the formation of fibrin mesh followed by collagen bands at 3 to 5 days, increasing until day 14.[8,9] Considering these data, we decided to evaluate adhesion formation on postoperative day 10. Prevention of permanent fibrous adhesions depends on the removal of this fibrin prior to its invasion by fibroblasts. However, we did not take any postoperative measure to clean the peritoneal cavity from the remaining fibrinous tissues such as blood. The fibrinous attachments naturally disappear by fibrinolysins released from peritoneal mesothelial cells. During the first 48 hours of healing of mesothelial defects, fibrinolytic activity is diminished by release of plasminogen activator inhibitors 1 and 2 from mesothelial, endothelial and inflammatory cells but thereafter it increases above normal levels.[27,28] Drugs that interfere with fibrinolytic activity can affect adhesion formation at the fibrin organization phase; whereas antiinflammatory drugs such as steroids can modulate later phases of the process, interfering with collagen formation. Octreotide might interfere with plasminogen activator inhibitor. Nevertheless, blood alone will not be able to induce adhesions.[29] These findings imply the presence of other factors in adhesion formation apart from those involved in fibrinogenesis theory. Postoperative adhesion formation may take place after all kinds of surgical traumas to the peritoneum irrespective of coagulation, suturing, abrasion or clamping of the tissues.[30,31] Adhesions develop when the integrity of the mesothelium is damaged and the concurrent ischemia occurs.[29] We created a peritoneal defect and visceral peritoneal injury by caecal abrasion for mesothelium damage and peritoneal trauma. This caused an almost complete adhesion formation that was prevented by octreotide therapy to some extent.

Although postoperative intraabdominal adhesions have largely been studied, limited information is available on the role of cytokines in adhesion formation. Kaidi, proposed TNF-α as a good biological marker for postoperative intraabdominal adhesion formation.[4] A marker that can detect patients who have intraabdominal adhesions would be very beneficial. TNF-α is a short-lived cytokine, produced early in the disease process, and is thus often undetectable in the serum of patients following admission.[32] Thus, we measured the portal vein and peritoneal fluid levels of cytokines. However, the level of IL-6 appears to be more stable and is raised in the serum of patients with acute pancreatitis, correlating to some degree with the severity of disease.[33,34] Alternatively, IL-6 may simply be a marker of more important proinflammatory mediators.[35] In our study, portal vein and peritoneal fluid TNF-α and IL-6 levels were higher in the control group compared to the sham group. Although the increased cytokine levels might be a harbinger of peritoneal adhesions, we did not look for a correlation between adhesion degree and cytokine levels. However, our result revealed that TNF-α and IL-6 levels increased due to the formation of intraperitoneal adhesion. In our study, despite a slight increase in peritoneal fluid TNF-α and IL-6 levels in the control groups compared to the sham group, the difference was not statistically significant. Octreotide also did not cause a reduction in peritoneal fluid cytokine levels. Reports suggest that somatostatin analogues have significant anti-inflammatory effects in vivo, associated with the suppression of proinflammatory cytokines and neuropeptides.[36] In inflammatory conditions

such as acute pancreatitis, excessive production of IL-6 from peripheral blood mononuclear cells may be altered by therapeutic intervention and could conceivably influence outcome.[35] Our results, although they were not statistically significant, showed that portal vein IL-6 and TNF-α levels were both considerably reduced by subcutaneous octreotide treatment. However, this effect of octreotide was not observed on peritoneal fluid IL-6 and TNF-α levels. This implied that TNF-α and IL-6 response to peritoneal injury was not mainly mesothelial cell origin.

Reports suggest that somatostatin analogues have significant antiinflammatory effects in vivo, associated with suppression of proinflammatory cytokines and neuropeptides.[36] Besides, it decreases the release of some growth factors, inhibits angiogenesis and prevents cell proliferation.[37-39] This also implies that somatostatin analogues such as octreotide may inhibit the inflammatory reaction which leads to intraperitoneal adhesion formation. Chao, showed that octreotide caused a significant reduction in the release of hydrogen peroxide, nitric oxide, and TNF-α from the macrophages.[40] Marton, detected a decrease in serum TNF-α and IL-6 levels in octreotide-treated rats with taurocholic acid-induced pancreatitis.[41] Chao, demonstrated in an in vivo study, that Kupffer cells treated with somatostatin, released significantly less amount of TNF-α than the untreated controls.[42] All studies of which TNF-α and IL-6 levels were measured in systemic blood demonstrate the suppressive effect of octreotide on cytokines. We also showed the suppressive effect of octreotide on portal vein blood TNF-α and IL-6 levels. This difference between the portal vein blood and peritoneal fluid cytokine response to peritoneal trauma revealed a selective effect of octreotide in the prevention of adhesion formation.

In conclusion, postoperative adhesion formation causes a significant increase in portal vein blood TNF-α and IL-6 levels. Octreotide has a selective effect on portal vein TNF-α and IL-6 levels and may prevent postoperative adhesion formation through the suppression of portal vein cytokine levels.

REFERENCES

1. Menzies D, Ellis H. Intestinal obstruction from adhesions: How big is the problem? Ann R Coll Surg Engl 1990;72:60-3.
2. Weibel MA, Majno G. Peritoneal adhesions and their relation to abdominal surgery. A postmortem study. Am J Surg 1973;126:345-53.
3. McKay CJ, Gallagher G, Brooks B, Imrie CW, Baxter JN. Increased monocyte cytokine production in association with systemic complications in acute pancreatitis. Br J Surg 1996;83:919-23.
4. Kaidi AA, Gurchumelidze T, Nazzal M, Figert P, Vanterpool C, Silva Y. Tumor necrosis factor-alpha: A marker for peritoneal adhesion formation. J Surg Res 1995;58:516-8.
5. Topley N, Petersen MM, Mackenzie R, et al. Human peritoneal mesothelial cell prostoglandin synthesis: Induction of cyclooxygenase mRNA by peritoneal macrophage-derived cytokines. Kidney Int 1994;46:900-9.
6. Topley N, Jorres A, Luttmann W, et al. Human peritoneal mesothelial cells synthesize interleukin-6: Induction by IL-1 beta and TNF alpha. Kidney Int 1993;43:226-33.
7. Topley N, Brown Z, Jorres A, et al. Human peritoneal mesothelial cells synthesize interleukin-8. Synergistic induction by interleukin-1 beta and tumor necrosis factor-alpha. Am J Pathol 1993;142:1876-86.
8. Milligan DW, Raftery AT. Observations on the pathogenesis of peritoneal adhesions: A light and electron microscopical study. Br J Surg 1974;61:274-80.
9. Raftery AT. Regeneration of parietal and visceral peritoneum: An enzyme histochemical study. J Anat 1976;121(Pt 3):589-97.
10. Sahin Y, Saglam A. Synergistic effects of carboxymethylcellulose and low molecular weight heparin in reducing adhesion formation in the rat uterine horn model. Acta Obstet Gynecol Scand 1994;73:70-3.
11. Kaleli B, Ozden A, Aybek Z, Bostanci B. The effect of L-arginine and pentoxifylline on postoperative adhesion formation. Acta Obstet Gynecol Scand 1998;77:377-80.
12. Levinson CJ, Swolin K. Postoperative adhesions: Etiology, prevention and therapy. Clin Obstet Gynecol 1980;23:1213-20.
13. Matucci-Cerinic M, Borrelli F, Gnereini S, et al. Somatostatin-induced modulation of inflammation in experimental arthritis. Arthritis Rheum 1995;38:1687-93.
14. O'Donnell LJ, Farthing MJ. Therapeutic potential of a long acting somatostatin analogue in gastrointestinal diseases. Gut 1989;30:1165-72.
15. Gry KE, Meier R. Pharmacodynamic effects of Sandostatin in the gastrointestinal tract. Digestion 1993;54 (Suppl 1):14-9.
16. Linsky CB, Diamond MP, Cunningham T, Constantine B, DeCherney AH, diZerega GS. Adhesion reduction in the rabbit uterine horn model using an absorbable barrier, TC-7. J Reprod Med 1987;32:17-20.

17. Rodgers K, Cohn D, Hotovely A, Pines E, Diamond MP, diZerega G. Evaluation of polyethylene glycol/polylactic acid films in the prevention of adhesions in the rabbit adhesion formation and reformation sidewall models. Fertil Steril 1998;69:403-8.
18. Operative Laparoscopy Study Group. Postoperative adhesion development after operative laparoscopy: Evaluation at early second-look procedures. Fertil Steril 1991;55:700-4.
19. Menzies D. Peritoneal adhesions. Incidence, cause and prevention. Surg Annu 1992;24(Pt 1):27-45.
20. Montz FJ, Shimaruki T, diZerega GS. Postsurgical mesothelial re-epithelization. In: DeCherney AH, Polan ML, eds. Reproductive Surgery. 1st ed. Chicago: Year Book; 1987. p.31-47.
21. Alatas E, Gural O, Alatas O, Colak O. Octreotide prevents postoperative adhesion formation by suppressing peritoneal myeloperoxidase activity. Hepatogastroenterology 2000;47:1034-6.
22. Lai HS, Chen Y. Effect of octreotide on postoperative intraperitoneal adhesions in rats. Scand J Gastroenterol 1996;31:678-81.
23. Baykal A, Ozdemir A, Renda N, Korkmaz A, Sayek I. The effect of octreotide on postoperative adhesion formation. Can J Surg 2000;43:43-7.
24. Hayry P, Aavik E, Myllarniemi M. Blockade of growth factor synthesis and growth factor action: Two possible sites of interference in allograft vessel disease and coronary bypass or balloon injury. Metabolism 1996;45:101-3.
25. Grant MB, Wargovich TJ, Ellis EA, Caballero S, Mansour M, Pepine CJ. Localization of insulin-like growth factor-1 and inhibition of coronary smooth muscle cell growth by somatostatine analogues in human coronary smooth muscle cells. A potential treatment for restenosis? Circulation 1994;89:1511-7.
26. Danesi R, Del Tacca M. The effects of somatostatin analog octreotide on angiogenesis in vitro. Metabolism 1996;45(8 Suppl 1):49-50.
27. Thompson JN, Paterson-Brown S, Harbourne T, Whawell SA, Kalodiki E, Dudley HA. Reduced human peritoneal plasminogen activating activity: Possible mechanism of adhesion formation. Br J Surg 1989;76:382-4.
28. Whawell SA, Wang Y, Fleming KA, Thompson EM, Thompson JN. Localization of plasminogen activator inhibitor-1 production in inflamed appendix by in situ m RNA hybridization. J Pathol 1993;169:67-71.
29. Bakkum EA, van Blitterswijk CA, Dalmeijer RA, Trimbos JB. A semiquantitative rat model for intraperitoneal postoperative adhesion formation. Gynecol Obstet Invest 1994;37:99-105.
30. McDonald MN, Elkins TE, Wortham GF, Stovall TG, Ling FW, McNeeley SG Jr. Adhesion formation and prevention after peritoneal injury and repair in the rabbit. J Reprod Med 1988;33:436-9.
31. Elkins TE, Stovall TG, Warren J, Ling FW, Meyer NL. A histologic evaluation of peritoneal injury and repair: Implications for adhesion formation. Obstet Gynecol 1987;70:225-8.
32. Banks RE, Evans SW, Alexander D, McMahon MJ, Whicher JT. Is fatal pancreatitis a consequence of excessive leukocyte stimulation? The role of tumor necrosis factor alpha. Cytokine 1991;3:12-6.
33. Viedma JA, Perez-Mateo M, Dominguez JE, Carballo F. Role of interleukin-6 in acute pancreatitis. Comparison with C-reactive protein and phospholipase A. Gut 1992;33:1264-7.
34. Leser HG, Gross V, Scheibenbogen C, et al. Elevation of serum interleukin-6 concentration precedes acute-phase response and reflects severity in acute pancreatitis. Gastroenterology 1991;101:782-5.
35. de Beaux AC, Ross JA, Maingay JP, Fearon KC, Carter DC. Proinflammatory cytokine release by peripheral blood mononuclear cells from patients with acute pancreatitis. Br J Surg 1996;83:1071-5.
36. Karalis K, Mastorakos G, Chroussos GP, Tolis G. Somatostatin analogues suppress the inflammatory reaction in vivo. J Clin Invest 1994;93:2000-6.
37. Woltering EA, Barrie R, O'Dorisio TM, et al. Somatostatin analogues inhibit angiogenesis in the chick chorioallantoic membrane. J Surg Res 1991;50:245-51.
38. Lehy T, Dubrasquet M, Bonfils S. Effect of somatostatin on normal and gastric-stimulated cell proliferation in the gastric and intestinal mucosae of the rat. Digestion 1979;19:99-109.
39. Pruthi RS, Farouk M, Tsai WH, Mishalopoulos G, Meyers WC. The effect of octreotide on hepatic regeneration in rats. Surgery 1993;113:84-9.
40. Chao TC, Cheng HP, Walter RJ. Somatostatin and macrophage function: Modulation of hydrogen peroxide, nitric oxide and tumor necrosis factor release. Regul Pept 1995;58:1-10.
41. Marton J, Szasz Z, Nagy Z, et al. Beneficial effect of octreotide treatment in acute pancreatitis in rats. Int J Pancreatol 1998;24:203-10.
42. Chao TC, Chao HH, Chen MF, Lin JD. Somatostatin modulates the function of Kupffer cells. Regul Pept 1997;69:143-9.