ANNALS OF SURGERY
Vol. 234, No. 2, 262–263

To the Editor:

We read with great interest the paper titled "Does Prophylactic Octreotide Decrease the Rates of Pancreatic Fistula and Other Complications after Pancreaticoduodenectomy?" by Charles Yeo et al,[1] and presented at the annual meeting of the American Surgical Association. However, we have some reservations on various aspects of the study design, analysis of data, and potential areas of bias.

1) The primary endpoints of the study were "pancreatic fistula, other complications and death," but it appears that a statistical power calculation was made only for pancreatic fistula. If, for example, "death" was also a primary study endpoint, and given the publications of the Baltimore group with a death rate of 1%, one would have needed more than 1,000 patients to be randomized to examine a difference in the death rate using octreotide.

2) In the discussion after the paper, the primary author admits to a bias on the premise that he expected a negative trial at the outset. In this context, it is pertinent to note that the study was terminated (by whom?) after recruitment of only 64% of the patients, which was probably insufficient to reach a statistically valid result.

3) Pancreatic fistula was judged on the tenth postoperative day or later. How was the primary endpoint recorded when more than 50% of patients were discharged on postoperative day 9 or earlier?

4) The authors state that the management of drains, including their removal, was left to the discretion of the primary attending surgeon. Did this study have any independent monitoring committee (excluding the primary author) that ensured a rigid implementation of the study protocol?

5) The trial was designed as a double-blind study. However, the "placebo" was saline and the first author states in the discussion that the octreotide injections were more painful than the saline injections. In the multicenter European trials,[2,3,4,5] taking into consideration the fact of pain at the injection site, the octreotide solvent that caused similar pain was used as a placebo. Thus, can the Yeo, et al. study be truly termed double-blind?

6) The withdrawal rate of this study was 45% (172 of 383) including 40 patients that were excluded because they did not receive "at least a 5-day course of octreotide study drug." How do the authors reconcile the study quality with the exclusion of these 40 patients from the final analysis? Against this background, how did the authors authenticate that the remaining patients received the study drug?

7) The authors state that "the octreotide and control saline placebo were identical in appearance, volume and labeling, thereby masking the nursing staff..." We are aware that octreotide (250 μg in a volume of 250 μL) is only available as a 5 ml vial and once opened, the stability is maintained for 2 weeks. Therefore, two 5 ml vials would be necessary for 22 injections (i.e., requirement of the study protocol) since a maximum of 20 injections are possible from a single vial. From the statement of costs incurred ($61/injection $\times$ 22 injections $\times$ 104 octreotide group patients = $139,568), it appears no octreotide was wasted. Does this imply that some patients shared the same 5 ml vial? If so, the double blind nature of the study is compromised.

The observations, based on our own past experience, raise an additional doubt; namely, that the study drug was repacked by the Investigational Drug Pharmacy from the commercially available 5 ml vials. If so, how was the therapeutic value of octreotide ensured? If the drug was not being replaced and the vials were not shared, then the stated costs incurred are greatly disproportionate to those mentioned in the article.

8) Regarding costs, the authors carefully present the exact costs involved for the whole study. They state that the "total cost of this study was $162,383." It has been mentioned that "the patients received the octreotide study drug subcutaneously before surgery." Becaues 383 patients were enrolled in this study, it is presumed that the study drug was prepared and reserved for all these patients. In this situation, we suspect that either the drug reserved for those 118 patients who underwent a total pancreatectomy was used for other study patients or the calculated costs in this study are incorrect. Through knowing that the first author is very precise in his cost analysis, there is obviously an error (because only 104 of 383 patients have been considered in the cost analysis, and the total comes to $139,568).

9) In 1999, the same authors published another randomized controlled trial (also presented at the American Surgical Association) about radical versus conservative pancreaticoduodenectomy.[6] In this paper, they state the study was conducted "between April 1996 and December 1997." They mentioned that "as part of an ongoing clinical trial evaluating pancreatic fistula and other complications, approximately 25% of the patients in this series received postoperative octreotide (250 μg subcutaneously every 8 hours) for 7 days."

A similar article by the same authors[7] states that "between January 1994 and December 1997 inclusive, pancreaticoduodenectomy was performed in 597 *consecutive* patients," and that "octreotide was not used prophylactically in these patients." However, in the 1999 paper,[6] the authors refer to the period between April 1996 and December 1997, and state that "as part of an ongoing clinical trial" comparing pancreaticoduodenectomy with and without extended retroperitoneal lymphadenectomy "approximately 25% of the patients in this series received postoperative octreotide."

In the present paper[1] there is no mention of these studies.[6,7] We agree with the authors conclusion that "in their setting" octreotide is not helpful and not cost-effective. However, we would appreciate clarification of the issues we have raised.

M. W. Büchler, MD
C. Bassi, MD
A. Fingerhut, MD
I. Klempa, MD
Bern, Switzerland
Verona, Italy
Poissy, France
Bremen, Germany

References

1. Yeo CJ, Cameron JL, Lillemoe KD, et al. Does prophylactic octreotide decrease the rates of pancreatic fistula and other complications after pancreaticoduodenectomy? Results of a prospective randomized placebo-controlled trial. Ann Surg 2000; 232:419–429.

2. Büchler M, Friess H, Klempa I, et al. Role of octreotide in the prevention of postoperative complications of elective pancreatic resection. Am J Surg 1992; 163:125–131.
3. Pederzoli P, Bassi C, Falconi M, et al. Efficacy of octreotide in the prevention of complications of elective pancreatic surgery. Italian Study Group. Br J Surg 1994; 81:265–269.
4. Montorsi M, Zago M, Mosca F, et al. Efficacy of octreotide in the prevention of pancreatic fistula after elective pancreatic resections: a prospective, controlled, randomized clinical trial. Surgery 1995;117: 26–31.
5. Friess H, Beger HG, Sulkowski U, et al. Randomized controlled multicentre study of the prevention of complications by octreotide in patients undergoing surgery for chronic pancreatitis. Br J Surg 1995; 82:1270–1273.
6. Yeo CJ, Cameron JL, Sohn TA, et al. Pancreaticoduodenectomy with or without extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma: comparison of morbidity and mortality and short-term outcome. Ann Surg 1999; 229:613–622.
7. Sohn TA, yeo CJ, Cameron JL, et al. Do preoperative biliary stents increase postpancreaticoduodenectomy complications? J Gastrointest Surg 2000; 4:258–267.

Author Reply:

We thank Drs. Büchler, Bassi, Fingerhut and Klempa for their letter and for their careful reading of our work. We appreciate the opportunity to clarify some issues with them.

THE ISSUE OF STUDY DESIGN AND ENDPOINTS

The trial was designed and carried out as a double blind study, as the octreotide/saline injections were not identifiable to the nurses or patients, and the individuals assessing for complications had no knowledge of whether the participants received octreotide or saline. While a few patients noted injection site pain, this did not disrupt the double blind status, nor lead to the discontinuation of the drug.

The primary endpoints that were analyzed were pancreatic fistula and other complications. Because there was only one patient in the study who died (in the octreotide group), our data cannot be considered of sufficient power to comment on the effect of octreotide on operative mortality.

Dr. Büchler and colleagues have questioned the definition of pancreatic fistula, particularly as it applies to patients discharged before postoperative day 10. Patients without evidence of a pancreatic leak on days 5, 6, or 7 had their drains removed and were discharged from the hospital. None were readmitted for leaks, abscesses, or anastomotic dehiscence. Patients whose drains were removed successfully before day 10 were considered *not* to have evidence of a pancreatic fistula.

As stated in the manuscript, the study was reviewed annually by an informal departmental Data Safety Monitoring Board and our Institutional Review Board. The decision to terminate the study was made by the former, when the data failed to reveal a benefit with the prophylactic use of octreotide.

THE ISSUE OF WITHDRAWAL RATE

While 383 patients scheduled to undergo pancreaticoduodenectomy were initially enrolled and randomized, the final study population consisted of 211 patients. As stated in the manuscript, 118 enrolled patients did not complete the study because they did not undergo pancreaticoduodenectomy, having unresectable disease or requiring lesser procedures. Fourteen enrolled patients underwent total pancreatectomy, and were not candidates to be continued in the study because they lacked a pancreatic anastomosis. Forty enrolled patients (10%) did not receive the appropriate octreotide/saline study drug for at least 5 days due to logistical and pharmacy issues, and were excluded from analysis.

THE ISSUE OF COSTS

The cost calculations printed in the manuscript have been reviewed and verified. Briefly, $22,815 was charged for study initiation, randomization and inventory management. The octreotide cost was $139,568, with octreotide vials being repackaged into unit dose syringes for individual dose administration. This cost reflects cost for octreotide purchase and pharmacy charges for repackaging into unit dose syringes. Of note, our cost analysis did not include the nursing costs and time for the study drug administration.

THE ISSUE OF STUDY OVERLAP

As part of our ongoing clinical trials here at Johns Hopkins, we have had the opportunity to include patients in numerous prospective randomized clinical trials. While there is unquestionably some overlap between trials, our trial designs are carefully reviewed to insure that we are not jeopardizing our data or its analysis. Concerning the octreotide study in question here, this study opened February 1998 and was closed to accrual February of 2000.

We hope our response will clarify the pertinent and important issues raised by Drs. Büchler, Bassi, Fingerhut, and Klempa. We are pleased that they concur that following pancreaticoduodenectomy, octreotide is “not helpful and not cost-effective.”ith D. Lillemoe, MD

Sincerely,

CHARLES J. YEO, MD
KEITH D. LILLEMOE, MD
JOHN L. CAMERON, MD

The following letter was accidentally published without its reply in the July 2001 issue of Annals of Surgery. *The original letter along with its reply have been reprinted here.*

To the Editor:

We read with interest the paper by Orozco et al[1] published in the August 2000 issue of the *Annals of Surgery*. Although we appre-

ciate the difficulties in carrying out this study comparing three established modalities of preventing recurrent variceal hemorrhage in patients with portal hypertension, we have certain reservations about the methodology and conclusions drawn. First, exclusion criteria are separately listed for the three modalities on trial. This would lead us to assume that patients were excluded after randomization to a particular arm that would affect the balance between the groups. For example, patients with gastric varices are excluded from sclerotherapy group. No mention is made of their exclusion from the pharmacotherapy group. It is well recognized that bleeding from fundal gastric varices is more severe and difficult to control compared to esophageal variceal bleeding.[2,3]

The exact etiology of the portal hypertension is not mentioned though the authors mention 'diverse hepatopathies.' It is not clear whether all patients were cirrhotic (biopsy proven). The large proportion of patients with anatomy unsuitable for shunt surgery (20/30) suggests that extrahepatic portal venous obstruction may be responsible for the portal hypertension in a large proportion in this group. If this was so, and the liver was normal in these cases, their prognosis would be better than that of patients with Child A cirrhosis as liver function is essentially normal.

Further, only 2 of the 46 patients subjected to endoscopic sclerotherapy are survivors without recourse to surgery. This is a far higher failure rate than reported in literature. Though initial endoscopic treatment is mentioned, little information is given about follow-up surveillance endoscopy. At our center, after initial obliteration, surveillance endoscopies are carried out 3 times per month for a year, then 6 monthly, and then yearly. Recurrent varices are resclerosed. The variceal recurrence rates are high, in the order of 60%, but post obliteration variceal rebleed rates are low, with few requiring surgery or dying of rebleed.[4,5] Acceptance of this surveillance regime is an important issue, especially in developing countries dealing with less educated patients.

The text states that 30 patients were operated on. In Table 1, only 25 patients are accounted for in the Childs grading. Furthermore it is suggested in Table 2 that the 2 patients in the surgical group with Childs C cirrhosis that rebled accounted for 22% of the population. However, Table 1 mentions that only 3 Childs C cirrhotics underwent surgery making the rebled rate 67%.

Not unsurprisingly, Childs A patients did better than Childs Group B and C patients. Not many surgeons would offer surgery for Childs C cirrhotics over a transjugular intrahepatic portosystemic shunt (TIPSS) owing to the associated high mortality.[6,7] Though the authors state that better results are obtained by surgery, this is not borne out in the survival curve shown in Figure 1 of the paper. Prolonging survival is the desired outcome rather than just a reduction in rebleeding.

Notwithstanding these limitations, the effort made by the authors must be lauded. We realize the difficulties of carrying out a randomized study between surgical and nonsurgical modalities at our center in a developing country, where consideration such as reliability of follow-up and ready availability of emergency care have to be taken into account before allocating patients to a sclerotherapy arm. We agree that non-shunting devascularization procedures give excellent immediate and long term results[6,8] and are the procedure of choice in patients with unsuitable venous anatomy.[9] In those willing to follow-up, low rebleed rates have been obtained with endoscopic sclerotherapy even on long term follow-up,[4,5] while surgery has its role, as stated by the authors, in patients with gastric varices as well as those rebleeding on sclerotherapy.

SUDEEP R. SHAH, MD
Gastroenterology Surgical Services
King Edward Memorial Hospital
Bombay, India

References

1. Orozco H, Mercado MA, Chan C, et al. A comparative study of the elective treatment of variceal hemorrhage with β-blockers, transendoscopic sclerotherapy and surgery. A prospective, controlled, and randomized trial during 10 years. Ann Surg 2000; 232:216–9.
2. Nagral S, Shah S, Gandhi M, et al. Bleeding isolated gastric varices: a retrospective analysis. Indian J Gastroenterol 1999; 18:69–72.
3. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology 1992; 16:1343–9.
4. Mathur SK, Naik SR, Supe AN, et al. Endoscopic esophageal variceal sclerotherapy using 3% aqueous phenol. Gastrointest Endosc 1992; 38:152–7.
5. Mathur SK, Shah SR. Endoscopic variceal sclerotherapy for patients with EHPVO: How effective is it in the long term? A study of patients completing 10 year followup. Hepatology 1999; 30:217A.
6. Mathur SK, Shah SR, Soonawala ZF, et al. Transabdominal extensive oesophagogastric devascularization with gastro-oesophageal stapling in the management of acute variceal bleeding. Br J Surg 1997; 84:413–7.
7. Jenkins SA, Shields R. Variceal haemorrhage after failed injection sclerotherapy: the role of emergency oesophageal transection. Br J Surg 1989; 76:49–51.
8. Mathur SK, Shah SR, Nagral SS, et al. Transabdominal extensive esophagogastric devascularization with gastroesophageal stapling for management of noncirrhotic portal hypertension: long-term results. World J Surg 1999; 23:1168–74.
9. Shah SR, Nagral SS, Mathur SK. Results of a modified Sugiura's devascularisation in the management of "unshuntable" portal hypertension. HPB Surg 1999; 11: 235–9.

Author Reply:

We appreciate the comments from Dr. Shah and Dr. Mathur. Indeed, there were exclusion criteria individualized for each therapeutic arm, so that if a contraindication to one therapeutic arm was found, it was randomized only for the remaining two. The design was done in this fashion to evaluate the real therapeutic effect of each arm, and not to affect the study with early dropouts. Patients excluded from the pharmacology group were those in which the cardiologist found a contraindication to the use of B-blockers. The etiology of portal hypertension is depicted in the table.

Not all patients excluded from a shunt operation had spleno meso portal thrombosis. When we talk about non-suitable anatomy for a shunt, we refer to patients with a small splenic vein or a tortuous vessel with evidence of recanalized thrombosis, as well as patients with an inadequate left renal vein (inadequate drainage or distance). We also, like Dr. Shah and Dr. Mathur, have much experience with prehepatic portal hypertension and normal livers. In this subset of patients we also had excellent results with ablative procedures.[1,2] These cases were not included in the study.

Table. THE ETIOLOGY OF PORTAL HYPERTENSION

	B-blocker	Sclerotherapy	Surgery
Alcoholic cirrhosis	17	26	8
Post hepatitic cirrhosis	21	18	16
Chronic hepatitis and autoimmune liver disease	2	2	6

The definition of failure was the reappearance of bleeding. These patients were changed to other treatment modalities early after the failure. We agree that some of the patients treated by means of endoscopy could have been treated with another attempt of sclerotherapy until obliteration could be obtained, but that was not the design of the study.

There is a mistake in the text and in table 1 that is completely our responsibility. In the surgical group there were 19 Child A patients, 3 Child B patients, and 8 (instead of 3) Child C patients. The text states that 7 of these 8 Child C patients died. Two of these patients had rebleeding as stated in table 2.

We also agree with Dr. Shah and Dr. Mathur that patients with bad liver function (Child C) should be excluded from surgical treatment. For those patients, a liver transplant is better. TIPS is also associated with a higher mortality in patients with bad liver function.

When the study was designed, we as surgeons felt that a significant difference was going to be found apart from rebleeding. We knew that surgery had a lower rebleeding rate and we wanted to show that this had an impact on survival. We were not able to show these as other groups either. Indeed, prolonged survival is the most desired outcome, and what we have shown is that surgery has an equal survival rate without bleeding. In the last 5 years, we have achieved a very low mortality (1%) with a low rebleeding rate (4% for shunt, 11% for devascularizations), and also a low encephalopathy rate in patients treated with portal blood flow preserving procedures. Also, a very good 5-year survival rate has been obtained.[3] This is the result of strict patient selection, versatility of the surgical procedures according to the anatomical status of the patient, and an experienced team in liver surgery. We feel that every liver transplant program can achieve the same results, because we are sure that liver transplant surgeons and anesthesiologists can perform portal hypertension surgery with a high success rate for patients with good liver function, and whose only problem is bleeding.

References

1. Orozco H, Takahashi T, Mercado MA, et al. Surgical management of extrahepatic portal hypertension and variceal bleeding. World J Surg 1994; 18:246–250.
2. Orozco H, Takahashi T, Mercado MA, et al. The Sugiura procedure for patients with hemorrhagic portal hypertension secondary to extrahepatic portal vein thrombosis. Surg Gynecol Obst 1991; 173:45–48.
3. Mercado MA, Orozco H, Ramirez-Cisneros F, et al. Diminished mortality in portal hypertension surgery. Reubication in therapeutic armamentarium. In press. Hector Orozco, MD Miguel Angel Mercado, MD Carlos Chan, MD

HÉCTOR OROZCO, MD
Portal Hipertension
Instituto Nacional de
Ciencias Medicas y Nutri
cion Salvador Zubiran
Mexico City, Mexico