증거수집 및 평가, 실천을 위한 체크리스트

아주대학교병원 내과
신 승 수

메드라인 또는 Cochrane library를 검색하기 위한 체크리스트

1 이미 알고 있는 특정 논문 검색을 위해 (제목, 초록 안에 있는) 단어나 저자, 제목, 연구기관명, 잡지명, 출판년도의 분야접미사를 이용한다.

2 주제를 대상으로 가장 적절한 검색을 위해 의학주제어표목(MeSH) 및 (제목, 초록의) 단어로 먼저 검색한 다음, 이 두 검색결과를 Boolan 연산자 "or"를 이용하여 합친다.

3 제한적인 (특정) 주제에 대한 검색을 위해 2에 의거한 검색을 두 번 이상 시행한 결과를 Boolan 연산자 "and"를 이용하여 합친다.

4 방법론상의 질이 높은 논문을 찾기 위해 치료적 처치, 원인, 진단적 수기, 역학 등 각각의 영역 또는 무작위화시험, 체계적 리뷰, 메타 분석과 같은 출판 형태를 구분할 수 있는 문자열을 이용하여 검색한다.

5 Boolan 연산자 "not"과 같은 것을 이용하여 부적절한 논문을 제거하는 등의 방법을 이용하여 이상의 검색결과를 세밀하게 구별한다.

6 색인의 오류 및 오분류가 흔하기 때문에 달리 방법이 없을 경우에 한하여 부표목(subheading)을 이용한 검색을 시행한다.

7 큰 검색결과의 범위를 50개 남짓한 논문으로 좁힌 다음에는 너무 기계적인 명령에만 의존하지 말고 스스로 논문의 초록을 살피면서 적절한 논문을 고른다.

이 논문이 무엇을 말하고 있는가를 판단하기 위한 체크리스트

1 왜 연구를 하였으며 저자가 검증한 가설은 무엇인가?

2 어떤 종류의 연구가 행해졌는가?

- 일차 연구(실험, 무작위화시험, 기타 임상시험, 코호트 연구, 환자-대조군 연구, 단면조사연구, 추적 연구, 증례보고, 증례시리즈)인가?
- 이차 연구(개관, 체계적 리뷰, 메타 분석, 의사결정 분석, 지침 개발, 경제학적

분석)인가?

3 특정 연구 영역(치료, 진단, 선별, 예후, 원인)에 맞는 연구설계인가?

4 연구가 윤리적인가?

논문의 방법론 체크리스트

1 독창적인 연구인가?

2 연구 대상은 누구인가?

- 어떻게 선정된 대상자인가?
- 누가 연구에 포함되고 제외되었는가?
- 현실적인 치료 환경에서 대상자 연구가 진행되었는가?

3 올바른 연구설계가 이루어졌는가?

- 연구 중 고려했던 특별한 처치나 연구 내용은 무엇이었으며 비교는 어떻게 하였는가?
- 어떤 결과를 어떻게 측정하였는가?

4 연구에서 통제가 잘 이루어졌는가?

- " 무작위화시험" 이었다면 무작위화 과정이 진정 무작위적으로 이루어졌는가?
- 코호트, 환자-대조군, 기타 비무작위화 비교시험이었다면 대조군이 적절하였는가?
- 특정 비교점을 제외한 나머지 부분이 비교군 사이에 동일하였는가?
- 결과 평가가 " 맹검적" 으로 이루어졌는가?

5 결과를 믿을 수 있을 정도로 연구 규모가 크고, 충분한 추적조사 기간을 가졌으며, 추적조사가 완결되었는가?

논문의 통계적인 면을 위한 체크리스트

1 연구 상황 설정이 제대로 되어 있는가?

- 대상 연구군들간에 비교성이 있는지 확인하였으며, 필요할 경우 차이가 나는 기본 특성을 보정하였는가?
- 어떤 형태의 자료가 있으며 자료 성격에 알맞은 통계 검정이 이루어졌는가?

- 만일 논문에서 좀처럼 사용하지 않는 통계검정을 하였다면 이를 선택한 이유와 참고문헌이 제시되어 있는가?
- 원래의 연구계획대로 자료를 분석하였는가?

2 짝지은 자료, 양측/단측 검정, 외딴 값:

- 짝지은 자료에 대해 짝지은 검정이 이루어졌는가?
- 처치 효과가 부정적인 쪽으로 작용하리라 추정되는 경우에서도 양측 검정을 하였는가?
- " 외딴값" 에 대해 상식과 적절한 통계학적 보정이 이루어진 채로 분석이 이루어졌는가?

3 상관, 회귀, 인과성:

- 상관분석이 회귀분석과 구별된 채로 이루어졌으며, 상관계수의 계산 및 해석이 제대로 이루어졌는가?
- 인과성의 법칙과 방향성에 대한 가정이 이루어졌는가?

4 확률, 신뢰구간:

- " p 값" 을 제대로 계산하고 해석하였는가?
- 신뢰구간이 계산되었고 저자들의 결론에 이것이 반영되어 있는가?

5 저자가 처치의 효과를 표현함에 있어 이것이 개별 환자들에게 편익으로 또는 위해로 작용할 것인지의 관점을 다음과 같은 도구를 가지고 말하였는가?

- 비교위험도감소(relative risk reduction)
- 절대위험도감소(absolute risk reduction)
- NNT(number needed to treat)
- 비차비(odds ratio)

진단 및 선별 검사의 타당도를 검토한 논문에 대한 체크리스트

1 이 검사는 내 임상 행위가 잠재적으로 당면한 문제인가?

2 진짜 황금 표준과 비교한 검사인가?

3 이 타당도 연구가 적절한 대상자의 범위를 포함하고 있는가?

4 work up bias를 피하였는가?

5 observer bias를 피하였는가?

6 검사를 같은 연구자 또는 다른 연구자가 재현할 수 있는가?

7 타당도 연구를 통해 얻은 그 검사의 특성이 어떠한가?

8 검사의 민감도, 특이도 및 다른 특성들에 대한 신뢰구간이 제시되었는가?

9 결과로부터 적절한 " 정상범위(normal range)" 를 이끌어 낼 수 있었는가?

체계적 리뷰, 메타 분석에 대한 체크리스트

1 평가하려는 리뷰가 중요한 임상적인 질문을 담고 있는 것인가?

2 적절한 데이터베이스 및 기타 중요한 자료원을 대상으로 철저한 검색이 행해졌는가?

3 방법론상의 질을 평가하였으며 각 임상시험에 대한 가중치부여가 적절하게 이루어졌는가?

4 리뷰 방법의 결과가 얼마나 민감한가?

5 숫적인 결과의 이해가 용이하고 문제가 요구하는 일반적인 측면에 상응하게 해석되었는가?

Calculation of sensitivity/specificity/LR

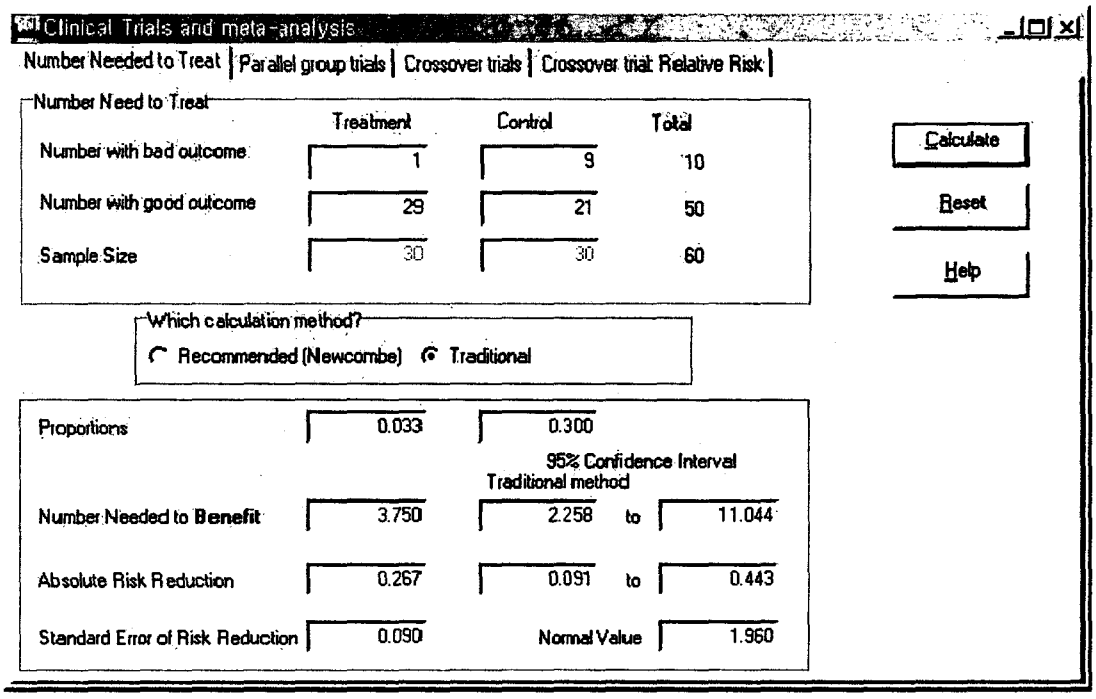
	Disease positive	**Disease negative**
Test positive	a	b
Test negative	c	d

Sensitivity = a/(a + c)
LR+ = [sensitivity/(1 – specificity)] = [a/(a + c)] ÷ [b/(b + d)]
Specificity = d/(b + d)
LR– = (1 – sensitivity)/specificity = [c/(a + c)] ÷ [d/(b + d)]
Positive predictive value = a/(a + b), negative predictive value = d/(c + d)
Pre-test probability = (a + c)/(a + b + c + d)

Calculations of OR/RR for use of trimethoprim-sulfamethoxazole prophylaxis in cirrhosis

	Adverse event occurs (infectious complication)		Adverse event does not occur (no infectious complication)		Totals	
Exposed to treatment (experimental)	1	a		29 b	a+b	30
Not exposed to treatment (control)	9	c		d 21	c+d	30
Totals	10	a+c	b+d	50	a+b+c+d	60

CER = c/(c+d) = 0.30
EER = a/(a+b) = 0.033
Control event odds = c/d = 0.43
Experimental event odds = a/b = 0.034
Relative risk = EER/CER = 0.11
Relative odds = odds ratio = (a/b)/(c/d) = ad/bc = 0.08



Calculations for the occurrence of diabetic retinopathy in IDDMs

Occurrence of diabetic neuropathy at 5 years among insulin-dependent diabetics in the DCCT trial		**Relative risk reduction (RRR)**	**Absolute risk reduction (ARR)**	**Number needed to treat (NNT)**
Usual insulin regimen (CER)	Intensive insulin regimen (EER)	$\frac{\lvert EER - CER \rvert}{CER}$	$\lvert EER - CER \rvert$	1/ARR
13%	38%	$\lvert 13\% - 38\% \rvert / 38\% = 66\%$	$\lvert 13\% - 38\% \rvert = 25\%$	1/25% = 4 pts, for 6 years, with intensive insulin Rx

증례 시나리오

김 ○ 수 남자/50세

직업: 회사원

음주력: 일주일에 한번, 소주 한 병 정도
흡연력: 담배 1/2갑/일×30년

10년 전 직장 건강검진에서 B형 간염 표면 항원(HBsAg) 양성이라는 이야기 처음 들었으나 이외에 특별한 만성 질환의 과거력 없었다. 이후 매 2년 간격으로 하는 직장 건강검진 때마다 같은 이야기 들었으나 별다른 증상 없어 더 이상 정밀검사 받지 않았다.

최근 발이 자주 붓고 쉽게 피곤한 증상이 발생하여 병원에 내원하여 시행한 혈액검사상 프로트롬빈타임의 증가(PT prolongation)와 저알부민혈증(hypoalbuminemia), 고빌리루빈혈증(hyperblirubinemia)이 있었고 복부초음파검사상 간경화와 비장비대, 중등도의 복수 소견 있었다. 전체적으로 Child-Pugh class C로 판단되었고, 식도정맥류 유무를 확인하기 위해 시행한 상부위장관 내시경상 Grade III의 식도정맥류 관찰되었다. 내시경 소견으로 보아 조만간 식도정맥류의 출혈가능성이 예상되었다. 환자는 식도정맥류의 출혈가능성을 두려워했고 이를 예방하기 위해서 어떻게 하는 것이 좋을지 담당의사에게 물었다.

담당 의사는 식도정맥류의 일차예방목적의 치료로서 베타차단제나 내시경적 식도정맥류결찰술 등이 사용될 수 있다는 이야기를 동료로부터 들었다. 따라서 이에 관련된 문헌을 고찰하고 자신의 판단을 바탕으로 과연 이런 치료법을 환자에게 권할 것인지, 만일 권한다면 이 중 무엇을 권할 것인지를 결정하기로 하였다.

문헌검색 및 고찰

본 문제의 해결을 위한 문헌의 검색 및 고찰을 위해 사용할 수 있는 의학주제어표목(MeSH)은 다음과 같다.

- Primary Prevention
- Esophageal Variceal Bleeding

이 두 의학주제어표목으로 인터넷 PubMed 사이트(http://www.ncbi.nlm.nih.gov/entrez)에 접속하여 문헌검색을 시작하였다.

각각의 의학주제어표목으로 검색한 두 결과를 검색명령어 " AND" 를 이용하여 검색범위를 좁혔고 다시 이를 " Randomized Controlled Trial" 로 범위를 좁혔다(그림 1). 그 결과 6개

NCBI PubMed National Library of Medicine NLM

PubMed Nucleotide Protein Genome Structure PopSet Taxonomy OMIM

Search PubMed for #1 AND #2 Preview Go

Clear

Limits Preview/Index **History** Clipboard

About Entrez

- Search History will be lost after one hour of inactivity.
- To combine searches use # before search number, e.g., #2 AND #6.
- Search numbers may not be continuous; all searches are represented.

Entrez PubMed
Overview
Help | FAQ
Tutorial
New/Noteworthy

PubMed Services
Journal Browser
MeSH Browser
Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Cubby

Related Resources
Order Documents
Grateful Med
Consumer Health
Clinical Alerts
ClinicalTrials.gov

Privacy Policy

Search	Most Recent Queries	Time	Result
#4	Search #1 AND #2Limits: Randomized Controlled Trial	09:22:10	6
#3	Search #1 AND #2	09:21:48	18
#2	Search esophageal variceal bleeding	09:21:16	2020
#1	Search primary prevention	09:20:42	64235

Clear History

Write to the Help Desk
NCBI | NLM | NIH
Department of Health & Human Services
Freedom of Information Act | Disclaimer

Limits: Randomized Controlled Trial

Display Summary Save Text Order Details Add tc

Show: 20 Items 1-6 of 6

1: Deschenes M, Barkun AN.
Comparison of endoscopic ligation and propranolol for the prir prevention of variceal bleeding.
Gastrointest Endosc. 2000 May;51(5):630-3. No abstract available.
PMID: 10896486 [PubMed - indexed for MEDLINE]

2: Avgerinos A, Armonis A, Manolakopoulos S, Rekoumis G, Argirakis G, Viazis N, Vlachogiannakos J, Adamopoulos A, Kanaghinis T, Raptis SA.
Endoscopic sclerotherapy plus propranolol versus propranolol primary prevention of bleeding in high risk cirrhotic patients wit esophageal varices: a prospective multicenter randomized trial
Gastrointest Endosc. 2000 Jun;51(6):652-8.
PMID: 10840295 [PubMed - indexed for MEDLINE]

3: Oberti F.
[Primary prevention of esophageal variceal rupture: endoscopi propranolol]?
Gastroenterol Clin Biol. 1999 Oct;23(10):1104-6. French. No abstract avail
PMID: 10592890 [PubMed - indexed for MEDLINE]

4: Sarin SK, Lamba GS, Kumar M, Misra A, Murthy NS.
Comparison of endoscopic ligation and propranolol for the prir prevention of variceal bleeding.
N Engl J Med. 1999 Apr 1;340(13):988-93.
PMID: 10099140 [PubMed - indexed for MEDLINE]

5: Plevris JN, Elliot R, Mills PR, Hislop WS, Davies JM, Bouchier IA, Hayes PC.
Effect of propranolol on prevention of first variceal bleed and s patients with chronic liver disease.
Aliment Pharmacol Ther. 1994 Feb;8(1):63-70.
PMID: 8186348 [PubMed - indexed for MEDLINE]

6: Duhamel O, Carle JP, Daures JP, Boyer A, Gislon J, Nalet B, Cassan P, Dubois A, Raffanel C, Balmes JL, et al.
[Primary prevention of digestive hemorrhage, caused by ruptur esophageal varices, by endoscopic sclerotherapy in patients w cirrhosis. Multicenter randomized controlled study].
Gastroenterol Clin Biol. 1994;18(1):57-62. French.
PMID: 8187990 [PubMed - indexed for MEDLINE]

Display Summary Save Text Order Details Add tc

COMPARISON OF ENDOSCOPIC LIGATION AND PROPRANOLOL FOR THE PRIMARY PREVENTION OF VARICEAL BLEEDING

SHIV K. SARIN, M.D., D.M., GURWANT S. LAMBA, M.D., D.M., MANDHIR KUMAR, M.D., D.M., ALOK MISRA, M.D., D.M., AND NANDAGUDI S. MURTHY, PH.D.

ABSTRACT

Background and Methods We compared propranolol therapy and endoscopic ligation for the primary prevention of bleeding from esophageal varices. This prospective, controlled trial included consecutive eligible patients who had large varices (>5 mm in diameter) that were at high risk for bleeding. The patients were assigned to either propranolol therapy, at a dose sufficient to decrease the base-line heart rate by 25 percent, or variceal ligation, to be performed weekly until the varices were obliterated or so reduced in size that it was not possible to continue treatment.

Results Of the 89 patients, 82 of whom had cirrhosis of the liver, 44 received propranolol and 45 underwent variceal ligation. The mean (±SD) duration of follow-up in each group was 14±9 and 13±10 months, respectively. The mean time required to achieve an adequate reduction in the heart rate was 2.5±1.7 days; the mean number of sessions needed to complete variceal ligation was 3.2±1.1. After 18 months, the actuarial probability of bleeding was 43 percent in the propranolol group and 15 percent in the ligation group (P=0.04). Twelve patients in the propranolol group and four in the ligation group had bleeding. Three of the four in the ligation group had bleeding before their varices had been obliterated. Nine patients in the ligation group had recurrent varices, a mean of 3.7 months after the initial treatment. Five patients in each group died; bleeding from the varices was the cause of death of four patients in the propranolol group and of three in the ligation group. There were no serious complications of variceal ligation; in the propranolol group, treatment was stopped in two patients because of side effects.

Conclusions In patients with high-risk esophageal varices, endoscopic ligation of the varices is safe and more effective than propranolol for the primary prevention of variceal bleeding. (N Engl J Med 1999;340: 988-93.)

©1999, Massachusetts Medical Society.

BLEEDING from esophageal varices is associated with mortality rates ranging from 30 to 70 percent.[1,2] Many therapies have been evaluated for primary prophylaxis against bleeding in people with cirrhosis and large varices.[3-5] The most effective therapy is the use of nonselective beta-blockers, which reduce the incidence of a first bleeding episode and, to some extent, reduce bleeding-related mortality.[5,6] However, beta-blockers have unpredictable effects on the hepatic venous pressure gradient, which is used to assess their efficacy.[7,8] Measurement of this gradient requires an invasive technique in which a catheter is passed through the femoral or jugular vein and wedged into a hepatic vein; the difference between the wedged and free hepatic venous pressures is recorded as the wedged hepatic venous pressure gradient. In one recent study,[9] the requisite reduction of more than 20 percent in the gradient was achieved in only 14 percent of patients who received propranolol. In another study, because of frequent side effects and contraindications, propranolol therapy was found suitable for only 23 percent of patients with cirrhosis.[10] Other issues of concern with respect to the use of beta-blockers are the lack of patient compliance, the prolonged (in some cases lifelong) need for therapy,[11] and the risk of rebleeding after the cessation of therapy.[12] The combination of a beta-blocker and a nitrate has been found superior to monotherapy with propranolol[13] or nadolol.[14] However, prolonged use of nitrates may increase the already advanced vasodilatory state of such patients[15] and increase mortality in patients with cirrhosis who are more than 50 years old.[16]

Endoscopic sclerotherapy is currently not recommended as prophylactic therapy for esophageal varices because of conflicting results in earlier studies.[17-19] Endoscopic variceal ligation is more effective and safer than sclerotherapy[20-22] and decreases the risk of initial bleeding[23] and the risk of death[24] due to varices as compared with no treatment. On the basis of these results, we conducted a prospective, randomized, controlled trial to compare the efficacy and safety of variceal ligation with those of propranolol for the primary prevention of variceal bleeding in patients with esophageal varices that were at high risk for bleeding.

METHODS

From September 1994 to July 1997, we screened 322 consecutive patients with portal hypertension who had never had bleeding from varices. Eligible patients included those with large, grade 3 or 4 varices as independently evaluated by two endoscopists and no history of hematemesis or melena.[23] The size of the varices was graded according to criteria published by Conn,[25] as follows: 1, small varices detectable only on performance of the Valsalva maneuver; 2, small varices (diameter, approximately 1 to 3 mm) visible during both phases of respiration; 3, varices of 3 to 6 mm; and 4, varices of >6 mm. The size of each varix was assessed by opening biopsy forceps in the lumen of the lower 2 to 3 cm of the esophagus. The risk of bleeding in large varices (>5 mm) was

From the Department of Gastroenterology, G.B. Pant Hospital (S.K.S., G.S.L., M.K., A.M.), and the Department of Biostatistics, Institute of Cytology and Preventive Oncology (N.S.M.) — both in New Delhi, India. Address reprint requests to Dr. Sarin at the Department of Gastroenterology, G.B. Pant Hospital, New Delhi 110 002, India, or at sksarin@nda.vsnl.net.in.

assessed by looking for the presence of at least one "red sign," such as a cherry-red spot, a red wale, or a hematocystic spot. The rate of agreement between the two observers with regard to red signs on endoscopy was 94 percent. For the same observer, the rate of agreement between two readings was 95 percent.

Cirrhosis was diagnosed on the basis of clinical, biochemical, histologic, or ultrasonographic evidence. Noncirrhotic portal fibrosis was diagnosed when varices were present and there was no evidence of thrombosis in the splenoportal axis on ultrasonography and no evidence of cirrhosis on liver biopsy.[26] Extrahepatic obstruction of the portal vein was diagnosed when a portal cavernoma was detected by ultrasonography and there were no signs of cirrhosis.[26,27] For all the patients, information on alcohol abuse was obtained, and tests for hepatitis B and C viruses and autoimmune markers in the serum were performed. The severity of liver disease was classified according to Child's criteria. Patients were excluded if they were receiving antiviral therapy or if they had concomitant hepatoma or another tumor, severe cardiopulmonary or renal disease, bradycardia (basal heart rate, <55 beats per minute), bronchial asthma, diabetes mellitus, heart failure, peripheral vascular disease, a psychiatric disorder, glaucoma, or prostatic hypertrophy. Written informed consent was obtained from the patients according to the guidelines of the 1975 Declaration of Helsinki.

Of the 105 patients with varices at high risk for bleeding who were recruited after screening, 90 were eligible for the study. Reasons for ineligibility were contraindications to the use of beta-blockers (eight patients), coexistent hepatoma (five), an inability on the part of the patient to attend follow-up (one), and refusal to follow the treatment protocol (one). Patients were randomly assigned at the time of the first endoscopic examination to undergo ligation or to receive propranolol, according to a table of random numbers.

Endoscopic Ligation

Patients assigned to the ligation group underwent ligation at the first endoscopy session or within the next 24 hours. After local application of lidocaine, an endoscope (model GIF X-Q 20 or CV-1, Olympus Optical, Tokyo) was introduced, and the ligation was carried out by placing a single rubber band (Bard Interventional Products, Tewksbury, Mass.) over a varix each time the endoscope was inserted. As many bands as possible (average, three to nine bands, with fewer in later sessions) were placed in the lower 5 to 7 cm of all variceal columns (vertical veins). Each residual varix was ligated distally and proximally to accelerate obliteration. A 25-cm-long sheath, supplied with the band-ligation set, was occasionally used as a sleeve over the endoscope to facilitate insertion and removal after the intravenous administration of 2.5 to 5.0 mg of diazepam.

Propranolol Therapy

Patients assigned to receive propranolol underwent base-line electrocardiography and cardiac evaluation after 15 minutes of rest. Treatment then began with the oral administration of 40 mg of propanolol. The heart rate and blood pressure were checked after 12 and 24 hours. Instead of adjusting the dose by monitoring the hepatic venous pressure gradient, we increased the dose in increments of 20 to 40 mg per day until a 25 percent decrease in the base-line heart rate was achieved. Treatment was stopped if any of the following occurred: systolic blood pressure less than 80 mm Hg, heart rate less than 55 beats per minute, or other serious side effects.

Follow-up

Patients were followed through July 1997. Endoscopic ligation was performed every week until the varices were obliterated or were reduced to a size of grade 1. In the latter instance, it was not possible to apply any more bands because of the small size of the varices. Patients were asked to record all symptoms, such as chest pain, fever, and dysphagia. The presence of ulcers or strictures was noted on endoscopy. After the varices had been obliterated or reduced in size to grade 1, patients underwent endoscopy monthly for the first three months and then once every three months until the end of follow-up. If varices recurred and became grade 2 in size or larger, ligation was repeated to obliterate them.

Patients receiving propranolol were monitored daily until beta-blockade was adequate, then monthly for the first three months, and subsequently every three months. Drug compliance was ascertained by interviewing the patient and by measuring the heart rate. Patients were advised to refrain from consuming alcohol and from taking nonsteroidal antiinflammatory drugs, histamine H_2 blockers, or proton-pump inhibitors.

End Points

The principal end point was bleeding from the varices. Additional end points included death due to variceal bleeding, causes related to the underlying liver disease, or unrelated causes; upper gastrointestinal tract bleeding from causes not related to the varices; or the development of serious side effects that required the discontinuation of therapy.

Bleeding

Any patient who had overt upper gastrointestinal bleeding during the study was admitted to the hospital and underwent endoscopy of the upper gastrointestinal tract within 24 hours to determine the source of bleeding. Bleeding from esophageal varices was diagnosed if active bleeding or a clot was seen on endoscopy or if there was evidence of recent bleeding in a patient with an esophageal varix and no other visible mucosal lesion. Bleeding was considered to have arisen from gastric varices if active bleeding or a clot was seen on endoscopy or if there was evidence of recent bleeding in a patient with a gastric varix and the bleeding had no other possible cause.[28] Bleeding was considered to be caused by portal hypertensive gastropathy if distinct lesions of the gastric mucosa were present and there was no evidence of bleeding from esophageal, gastric, or ectopic varices.[29] Bleeding was considered to be caused by esophageal ulcers as a result of band ligation if there was active bleeding or if there was an adherent clot on the esophageal ulcer. Bleeding from any source was considered to be serious if the estimated total blood loss was greater than 1500 ml, the heart rate was greater than 100 beats per minute, the systolic blood pressure was less than 100 mm Hg, and the patient required transfusion of more than 4 units of blood in six hours.

Management of Upper Gastrointestinal Tract Bleeding

All episodes of upper gastrointestinal tract bleeding were managed with supportive therapy, including transfusions of blood and plasma, balloon tamponade, infusion of somatostatin, or emergency ligation. Other complications of liver disease, such as hepatic encephalopathy and spontaneous bacterial peritonitis, were managed according to standard protocols.

Statistical Analysis

Data were analyzed according to an intention-to-treat strategy. Quantitative data were expressed as means (±SD) or as medians. Student's two-tailed t-test or an appropriate nonparametric test was used to compare values in the two groups. Qualitative data were analyzed by the chi-square test or Fisher's exact test.[30] Agreement between observers with regard to the red signs on endoscopy was measured by the kappa statistic.[31] The actuarial probabilities of bleeding from varices and of death from bleeding or any cause related to liver disease were calculated for all the patients by the Kaplan–Meier method, and comparisons were made with use of the log-rank test.[31] Subgroups were also analyzed, after patients without cirrhosis were excluded. Cox proportional-hazards regression analysis was carried out to assess the effect of confounding variables.[32]

RESULTS

The 90 eligible patients were randomly assigned to undergo ligation (46 patients) or to receive pro-

pranolol therapy (44 patients). One patient assigned to the ligation group failed to appear the next day and hence was excluded, leaving 45 patients in that group. The patients' characteristics are shown in Table 1. The mean dose of propranolol was 70±35 mg per day, and the time required to achieve an adequate reduction in the heart rate was 2.5±1.7 days. In the ligation group, obliteration of the varices was achieved in all the surviving patients with 3.2±1.1 endoscopy sessions over a period of 4.1±2.0 weeks. The endoscopy session was postponed by one week in the case of four patients because of diffuse ulcerations on the varices. On nine occasions, patients missed an endoscopy appointment. During the study period, bleeding occurred in 12 patients in the propranolol group and 4 in the ligation group (27 percent and 9 percent, respectively). The cumulative probability of variceal bleeding during different follow-up periods is shown in Figure 1. It was 43 percent in the propranolol group and 15 percent in the ligation group after 18 months of follow-up (P=0.04 by the log-rank test). No further events occurred after 18 months of follow-up, although only a few patients were followed for 32 months. The hazard ratio for variceal bleeding in the propranolol group, as compared with the ligation group, was 3.0 (95 percent confidence interval, 1.3 to 9.3). After adjustment for age, the ratio was 2.6 (95 percent confidence interval, 1.0 to 8.2).

TABLE 1. CHARACTERISTICS OF THE 89 PATIENTS ACCORDING TO STUDY GROUP.*

CHARACTERISTIC	ENDOSCOPIC LIGATION (N=45)	PROPRANOLOL (N=44)
Age — yr	44±12	39±17
Sex — no. (%)		
Male	33 (73)	32 (73)
Female	12 (27)	12 (27)
Cause of varices — no. (%)		
Cirrhosis	41 (91)	41 (93)
Alcoholic	11	9
Hepatitis B	16	15
Hepatitis C	5	2
Hepatitis B and C	0	1
Autoimmune	2	2
Cryptogenic	7	12
Extrahepatic portal-vein obstruction	3 (7)	3 (7)
Noncirrhotic portal fibrosis	1 (2)	0
Observations on endoscopy — no. of patients (%)		
Grade of varices		
III	32 (71)	34 (77)
IV	13 (29)	10 (23)
Gastric varices		
Before therapy	8 (18)	9 (20)
After therapy	9 (20)	9 (20)
Portal gastropathy		
Before therapy	9 (20)	10 (23)
After therapy	11 (24)	10 (23)
Gastric antral vascular ectasia		
Before therapy	0	2 (5)
After therapy	0	2 (5)
Child's classification — no. (%)		
A	7 (16)	9 (20)
B	23 (51)	22 (50)
C	15 (33)	13 (30)
Ascites — no. (%)	31 (69)	27 (61)
Encephalopathy — no. (%)	7 (16)	6 (14)
Abnormal prothrombin time — no. (%)†	33 (73)	29 (66)
Follow-up — mo	13±10	14±9

*Plus–minus values are means ±SD.

†The prothrombin time was considered abnormal if it was more than three seconds longer than the control value.

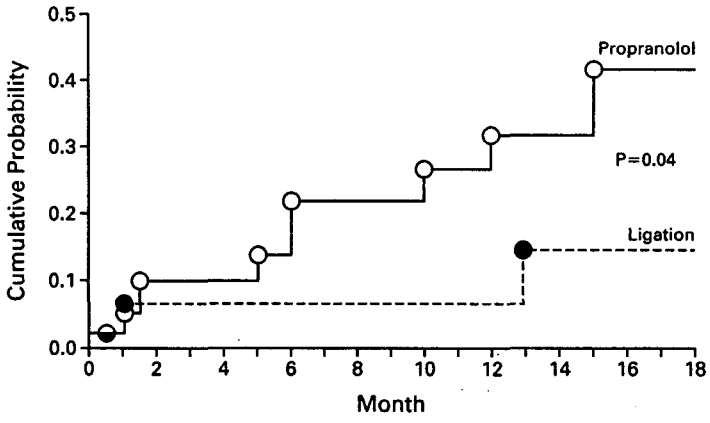
In three of the four patients in the ligation group who had bleeding, the bleeding occurred within the first six weeks, before the varices could be eradicated. The bleeding originated from post-ligation ulcers in two patients and from a recurrence of esophageal varices in one patient. In the patients in the propranolol group, bleeding from esophageal varices occurred throughout the treatment period. The severity of bleeding was similar in the two groups. The response to either therapy did not change if gastric varices were present; none of the patients had bleeding from gastric varices.

The 4 patients in the ligation group and 10 of the 12 patients in the propranolol group who had bleeding had advanced liver disease (Child's class B or C). None of the patients with noncirrhotic portal hypertension had bleeding. A subgroup analysis after data on patients without cirrhosis were excluded (leaving 41 patients in each group) showed actuarial probabilities of bleeding of 17 percent in the group undergoing ligation and 43 percent in the group receiving propranolol (P=0.08).

Ten patients (five in each group) died, all from disorders involving the liver (Table 2). The number of deaths related to bleeding was similar in the two groups: three patients in the ligation group and four in the propranolol group died from bleeding. The actuarial probability of survival in the ligation and propranolol groups was 88 percent and 82 percent, respectively (P=0.98). There was a trend toward fewer hospitalizations in the ligation group, and fewer patients in the ligation group required blood transfusions.

At the end of the follow-up period, 9 of 40 (22 percent) surviving patients in the ligation group had recurrent varices. Varices recurred a mean of 3.7±2.1 months (range, 2 to 13) after the initial obliteration and could be obliterated again in 1.4±0.5 sessions by repeated ligation. Second recurrences were rare during follow-up. In one patient, whose follow-up was irregular, bleeding occurred from large varices after 13 months; this patient subsequently died.

No serious complications resulted from variceal ligation. Transient retrosternal pain, fever, and dysphagia developed in 18 percent, 7 percent, and 4 percent



No. of Patients at Risk							
Ligation	45	40	27	16	12	8	7
Propranolol	44	35	28	16	13	7	5
No. of Patients with Failure of Therapy							
Ligation	—	3	3	3	3	4	4
Propranolol	—	5	9	9	11	12	12

Figure 1. Cumulative Probability of Variceal Bleeding in the Two Groups of Patients.

of the patients, respectively. Post-ligation variceal ulcers, generally superficial, developed in 36 patients (80 percent) one week after the first session of ligation. Sixteen patients in the propranolol group (36 percent) had one or more side effects possibly related to the drug. These included lethargy in 12 patients, psychiatric disturbances in 4, hypotension in 2, impotence in 2, and bronchospasm in 1. However, in only two of these patients was the therapy stopped, in one because of persistent hypotension, weakness, and lethargy and in the other because of altered sensorium possibly associated with propranolol therapy.

DISCUSSION

Treatment with beta-blockers[5,6] and endoscopic variceal ligation[23] have independently been shown to decrease the risk of a first episode of variceal bleeding. Our study confirmed these observations when the risk of bleeding in patients given either therapy was compared with that in untreated patients described in earlier studies. In one earlier study,[23] we found that the incidence of variceal bleeding in patients with untreated varices at high risk for bleeding was about 39 percent during a mean follow-up period of 14 months. Lay et al. observed incidence rates of variceal bleeding of 40 percent and 60 percent at 12 and 24 months of follow-up, respectively, in patients with untreated cirrhosis who had high-risk varices.[24] With the use of beta-blockers, this risk was decreased to 18 to 25 percent,[33,34] and with the addition of nitrates, to about 8 percent.[16]

We found that the risk of bleeding with ligation was significantly lower than that with propranolol therapy. The actuarial risk of bleeding at the end of 18 months in the ligation group was 15 percent, a risk similar to that reported previously with drug therapy.[16,33,34] The four patients in the ligation group who had bleeding had advanced liver disease. Severe early rebleeding from esophageal varices after ligation has been reported by Sakai et al.[35] and by Lay et al.[24] in patients with advanced liver disease. Two patients had bleeding from post-ligation ulcers and one from esophageal varices before the varices were obliterat-

Table 2. Outcomes of Treatment According to Study Group.

Characteristic	Endoscopic Ligation (N=45)	Propranolol (N=44)	P Value
Patients hospitalized — no. (%)	5 (11)	12 (27)	0.09
No. of patients needing blood transfusion	1	7	0.03
Mean no. of transfusions per patient	0.1	0.4	0.03
Actuarial probability of survival at 18 mo — %	88	82	0.98
Deaths — no. (%)	5 (11)	5 (11)	0.77
Cause of death — no.			
Bleeding*	3	4	
Spontaneous bacterial peritonitis	1	0	
Hepatic encephalopathy	1	1	
Child's class at time of death — no.			
A	0	0	
B	1	3	
C	4	2	

*Death was due to massive bleeding or was related to a bleeding event.

ed. Had we treated our patients with sucralfate[36] or omeprazole,[37] the two ulcer-related bleeding episodes might have been prevented. The only patient who had bleeding after variceal obliteration had irregular follow-up and missed a few endoscopy sessions scheduled for surveillance. In this patient, grade 3 varices developed, from which she had fatal bleeding. Varices recurred during follow-up in the ligation group a mean of 3.7±2.1 months (range, 2 to 13) after the initial obliteration. However, after repeated ligation, a second recurrence was rare. We therefore recommend that surveillance endoscopy should first be performed within three months after the obliteration of varices. Subsequently, endoscopy should be performed at six-to-nine-month intervals.

Beta-blocker therapy needs to be given for a prolonged period, possibly for life, and noncompliance raises the risk of bleeding to pretreatment levels.[11,12] In contrast, with ligation, varices can be obliterated within about a month, or possibly earlier, and therefore ligation offers a distinct advantage over lifelong propranolol therapy. Furthermore, no patient in our ligation group had to be excluded, whereas in the propranolol group eight patients had to be initially excluded because of contraindications to the drug and two subsequently withdrawn from therapy because of side effects. Others have also reported a high frequency of side effects, often requiring discontinuation of beta-blockers.[9-14]

The overall mortality in the two groups was similar (11 percent), although fewer patients in the ligation group required blood transfusions and there was a trend in that group toward fewer hospitalizations. Ligation should have a role particularly in the treatment of patients with high-risk varices in whom beta-blockers are contraindicated or must be discontinued because of side effects.[38] Our findings also suggest that the combination of both therapies should be evaluated to determine whether even better results can be achieved.

Part of this work has appeared in abstract form (*Hepatology* 1997;26: 360A).

REFERENCES

1. Christensen E, Fauerholdt L, Schlichting P, Juhl E, Poulsen H, Tygstrup N. Aspects of the natural history of gastrointestinal bleeding in cirrhosis and the effect of prednisone. Gastroenterology 1981;81:944-52.
2. Smith JL, Graham DY. Variceal hemorrhage: a critical evaluation of survival analysis. Gastroenterology 1982;82:968-73.
3. Conn HO, Lindenmuth WW, Mav CJ, Ramsby GR. Prophylactic portacaval anastomosis. Medicine (Baltimore) 1972;51:27-40.
4. Paquet KJ. Prophylactic endoscopic sclerosing treatment of the esophageal wall in varices: a prospective controlled randomized trial. Endoscopy 1982;14:4-5.
5. Poynard T, Calès P, Pasta L, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. N Engl J Med 1991;324:1532-8.
6. D'Amico G, Pagliaro L, Bosch J. The treatment of portal hypertension: a meta-analytic review. Hepatology 1995;22:332-54.
7. Groszmann RJ, Bosch J, Grace ND, et al. Hemodynamic events in a prospective randomized trial of propranolol versus placebo in the prevention of a first variceal hemorrhage. Gastroenterology 1990;99:1401-7.
8. Feu F, Garcia-Pagan JC, Bosch J, et al. Relation between portal pressure response to pharmacotherapy and risk of recurrent variceal haemorrhage in patients with cirrhosis. Lancet 1995;346:1056-9.
9. Bañares R, García-Pagán JC, Piqueras B, et al. Carvedilol, a new nonselective β-blocker with intrinsic α-adrenergic activity, has a greater portal hypertensive effect than propranolol in patients with cirrhosis. Hepatology 1997;26:Suppl:133A. abstract.
10. Silvain C, Chauvin C, Verneau A, Carretier M, Beauchant M. Combien de cirrhotique sont-ils susceptibles d'être traite par le propranolol au décours d'une hémorragie digestive? Gastroenterol Clin Biol 1985;9:670-3.
11. Sarin SK. Long term management of esophageal varices. Drugs 1992; 44:Suppl 2:56-69.
12. Lebrec D, Bernuau J, Rueff B, Benhamou J-P. Gastrointestinal bleeding after abrupt cessation of propranolol administration in cirrhosis. N Engl J Med 1982;307:560.
13. Garcia-Pagan JC, Feu F, Bosch J, Rodes J. Propranolol compared with propranolol plus isosorbide-5-mononitrate for portal hypertension in cirrhosis: a randomized controlled study. Ann Intern Med 1991;115:869-73.
14. Merkel C, Marin R, Enzo E, et al. Randomised trial of nadolol alone or with isosorbide mononitrate for primary prophylaxis of variceal bleeding in cirrhosis. Lancet 1996;348:1677-81.
15. Groszmann RJ. Beta-adrenergic blockers and nitrovasodilators for the treatment of portal hypertension: the good, the bad, the ugly. Gastroenterology 1997;113:1794-7.
16. Angelico M, Carli L, Piat C, Gentile S, Capocaccia L. Effects of isosorbide-5-mononitrate compared with propranolol on first bleeding and long-term survival in cirrhosis. Gastroenterology 1997;113:1632-9.
17. The Veterans Affairs Cooperative Variceal Sclerotherapy Group. Prophylactic sclerotherapy for esophageal varices in men with alcoholic liver disease: a randomized, single-blind, multicenter clinical trial. N Engl J Med 1991;324:1779-84.
18. Fardy JM, Laupacis A. A meta-analysis of prophylactic endoscopic sclerotherapy for esophageal varices. Am J Gastroenterol 1994;89:1938-48.
19. Paquet K-J, Kalk J-F, Klein C-P, Gad H-A. Prophylactic sclerotherapy for esophageal varices in high-risk cirrhotic patients selected by endoscopic and hemodynamic criteria: a randomized, single-center controlled trial. Endoscopy 1994;26:734-40.
20. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. Ann Intern Med 1995;123:280-7.
21. Sarin SK, Govil A, Jain AK, et al. Prospective randomized trial of endoscopic sclerotherapy versus variceal band ligation for esophageal varices: influence on gastropathy, gastric varices and variceal recurrence. J Hepatol 1997;26:826-32.
22. Stiegmann GV, Goff JS, Michaletz-Onody PA, et al. Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. N Engl J Med 1992;326:1527-32.
23. Sarin SK, Guptan RK, Jain AK, Sundaram KR. A randomized controlled trial of endoscopic variceal band ligation for primary prophylaxis of variceal bleeding. Eur J Gastroenterol Hepatol 1996;8:337-42.
24. Lay CS, Tsai Y-T, Teg C-Y, et al. Endoscopic variceal ligation in prophylaxis of first variceal bleeding in cirrhotic patients with high-risk esophageal varices. Hepatology 1997;25:1346-50.
25. Conn HO. Ammonia tolerance in the diagnosis of esophageal varices: a comparison of the endoscopic, radiologic and biochemical techniques. J Lab Clin Med 1967;70:442-51.
26. Sarin SK, Sundaram KR, Ahuja RK. Predictors of variceal bleeding: an analysis of clinical, endoscopic, and haemodynamic variables, with special reference to intravariceal pressure. Gut 1989;30:1757-64.
27. Sarin SK. Non-cirrhotic portal fibrosis. Gut 1989;30:406-15.
28. Sarin SK, Lahoti D, Saxena SP, Murthy NS, Makwana UK. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. Hepatology 1992;16: 1343-9.
29. Sarin SK, Sreenivas DV, Lahoti D, Saraya A. Factors influencing development of portal hypertensive gastropathy in patients with portal hypertension. Gastroenterology 1992;102:994-9.
30. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1977;35:1-39.
31. Altman DG. Practical statistics for medical research. London: Chapman & Hall, 1991.
32. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34: 187-220.
33. Pascal J-P, Cales P, Multicenter Study Group. Propranolol in the prevention of first upper gastrointestinal tract hemorrhage in patients with cir-

rhosis of the liver and esophageal varices. N Engl J Med 1987;317:856-61. [Erratum, N Engl J Med 1988;318:994.]
34. The Italian Multicenter Project for Propranolol in Prevention of Bleeding. Propranolol for prophylaxis of bleeding in cirrhotic patients with large varices: a multicenter, randomized clinical trial. Hepatology 1988;8:1-5.
35. Sakai P, Maluf Filho F, Melo JM, Ishioka S. Is endoscopic variceal band ligation of esophageal varices contraindicated in Child-Pugh C patients? Endoscopy 1994;26:511-2.
36. Polson RJ, Westaby D, Gimson AES, et al. Sucralfate for the prevention of early rebleeding following injection sclerotherapy for esophageal varices. Hepatology 1989;10:279-82.
37. Gimson A, Polson R, Westaby D, Williams R. Omeprazole in the management of intractable esophageal ulceration following injection sclerotherapy. Gastroenterology 1990;99:1829-31.
38. Shahi HM, Sarin SK. Prevention of first variceal bleed: an appraisal of current therapies. Am J Gastroenterol 1998;93:2348-58.

치료논문의 평가

치료논문의 평가를 위해 논문에 담긴 다음 항목들을 찾아보고 이를 평가해본다.

1. 임상시험의 결과는 타당한가?
    - 무작위배정이 이루어졌는가?
    - 추적관찰은 충분히 완결되었는가?
    - 모두 애초에 배정된 군에 따라 분석하였는가?
    - 이중맹검법이 시행되었는가?
    - 각군은 치료방법의 차이 외에 모든 면에서 동일하게 취급되었는가?
    - 각군은 임상시험의 시작단계에서 유사하였는가?
2. 해당 연구의 결과가 얼마나 임상적으로 중요한가?
    - 치료의 효과는 어느 정도인가?

	CER	EER	RRR : (CER-EER)/CER	ARR : (CER-EER)	NNT : (1/ARR)
Esophageal variceal bleeding					

    - 치료에 따른 부작용은 어느 정도인가?

	CER	EER	RRI : (CER-EER)/CER	ARI : (CER-EER)	NNH : (1/ARI)
Complications					

3. 해당 연구결과를 실제 내 환자에게 적용할 수 있는가?
    - 내 환자와 연구대상간에 차이가 존재하는가?
    - 실행 가능한 치료법인가?
    - 연구대상자와 내 환자의 차이를 보정할 필요가 있는가?
        - F factor를 구한다.
            - F factor for treatment
            - F factor for harm
        - F factor를 이용하여 실제 내 환자의 NNT, NNH를 구한다.

- ◆ 실제 NNT = NNT/F
- ◆ 실제 NNH = NNH/F

- 치료법 자체와 치료의 결과가 실제 환자에게 가지는 가치와 기대는 무엇인가?
  - ■ S factor를 구한다.
    - ◆ 치료하지 않은 결과

      사망(0) ---------- 건강/완치(1)
    - ◆ 부작용의 수용

      수용못함(0) ---------- 수용함(1)
    - ◆ S factor
- 해당 치료법을 적용시 실제 환자에서 기대되는 잠재적인 편익과 손실은 무엇인가?
  - ■ LHH(likelihood of being helped vs. harmed)를 구한다.
    - ◆ LHH = (1/NNT)× F× S : (1/NNH)× F