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• BRIEF REPORTS •

Meta analysis of propranolol effects on gastrointestinal hemorrhage in cirrhotic patients

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Abstract

AIM: To assess the effects of propranolol as compared with placebo on gastrointestinal hemorrhage and total mortality in cirrhotic patients by using meta analysis of 20 published randomized clinical trials.

METHODS: A meta analysis of published randomized clinical trials was designed. Published articles were selected for study based on a computerized MEDLINE and a manual search of the bibliographies of relevant articles. Data from 20 relevant studies fulfilling the inclusion criteria were retrieved by means of computerized and manual search. The reported data were extracted on the basis of the intention-to-treat principle, and treatment effects were measured as risk differences between propranolol and placebo. Pooled estimates were computed according to a random-effects model. We evaluated the pooled efficacy of propranolol on the risk of gastrointestinal hemorrhage and the total mortality.

RESULTS: A total of 1 859 patients were included in 20 trials, 931 in the propranolol groups and 928 as controls. Among the 652 patients with upper gastrointestinal tract hemorrhage, 261 patients were treated with propranolol, and 396 patients were treated with placebo or non-treated. Pooled risk differences of gastrointestinal hemorrhage were -18 % [95 % CI, -25 %, -10 %] in all trials, -11 % [95 % CI, -21 %, -1 %] in primary prevention trials, and -25 % [95 % CI, -39 %, -10 %] in secondary prevention trials. A total of 440 patients died, 188 in propranolol groups and 252 in control groups. Pooled risk differences of total death were -7 % [95 % CI, -12 %, -3 %] in all trials, -9 % [95 % CI, -18 %, -1 %] in primary prevention trials, and -5 % [95 % CI, -9 %, -1 %] in secondary prevention trials.

CONCLUSION: Propranolol can markedly reduce the risks of both primary and recurrent gastrointestinal hemorrhage, and also the total mortality.

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INTRODUCTION

Gastrointestinal hemorrhage due to portal hypertension is a leading cause of death in patients with cirrhosis. The first episode of bleeding is fatal in 40 % to 50 % of such patients and two-thirds die within 1 year. It has been shown that treatment with propranolol can reduce portal venous pressure[1], portal blood flow[2] and superior portosystemic collateral blood flow[3] and its efficacy on preventing gastrointestinal hemorrhage has been assessed in many randomized clinical trials. Some trials have been primary, in which the drug was used to prevent hemorrhage in patients who have not bled, some have been secondary with the drug used to prevent rebleeding. Numerous primary and secondary prevention studies concluded that propranolol treatment decreased the incidence of gastrointestinal hemorrhage. Thus far, however, randomized clinical trials usually included small sample sizes and showed conflicting results, which hindered researchers drawing conclusions from the trials.

In meta analysis each treated group is compared with controls from the same study, and the treatment effect is combined across all studies, to provide information both about the presence of any significant effect and about its size. We have made extensive efforts to find all relevant studies by means of computerized and manual search. Then we combined all the studies including primary and secondary, to assess the effectiveness of propranolol as compared with placebo on the prevention of gastrointestinal hemorrhage.

MATERIALS AND METHODS

This meta analysis was performed according to a protocol determined before the study, and the widely accepted methodological recommendations[4-6]. Measurement of treatment effectiveness was determined on the basis of primary or recurrent gastrointestinal hemorrhage, and mortality.

Selection of trials

Studies that fulfilled the following criteria were included in the present meta analysis: (a) propranolol was compared with placebo; (b) patients were randomly assigned to the treatment regimen, and studies were prospective; (c) patients with cirrhosis of liver were included; (d) outcomes of primary or recurrent bleeding, and death were assessed; (e) results were published as abstracts or full reports.

Study identification

Pertinent studies were retrieved from MEDLINE database by using the search terms "propranolol", "cirrhosis" and "gastrointestinal hemorrhage" and by limiting the search to reports of clinical trials and studies with human patients. In addition, a manual search was performed by checking the reference lists from articles or reviews to identify studies not yet included in MEDLINE database. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the meta-analysis. Finally, twenty randomized clinical trials that fulfilled the criteria were identified, fifteen were published in full form[7-21], and five in abstract form[22-26].

Data extraction

Data from each randomized clinical trial were extracted by two independent reviewers (Jin-Wei Cheng, Liang Zhu). For each study and each type of treatment, the following data were extracted: number of patients, and number of each outcome. Numeric discrepancies between the two independent data extractions were resolved after discussion.

Statistical methods

All comparisons were performed according to the randomly assigned treatment (intended-treatment analysis). Because of different clinical characteristics among study groups, and varying sample sizes, we assumed that heterogeneity was present even not statistically significant, and we decided to combine data by using a random-effects model to achieve more conservative estimates[27].

For all the outcomes, the pooled estimates were computed with the method of DerSimonian and Laird[27]. Summary point estimates and 95 % confidence interval (CI) were reported. Risk differences less than zero denoted an advantage for propranolol. Those more than zero denoted an advantage for placebo. 95 % CIs of risk differences not including 0 denoted a statistically significant advantage.

RESULTS

All trials

A total of 1 859 patients were included in the twenty trials, 931 in the propranolol groups and 928 as controls.

Table 1 Point estimates and 95 % CIs of the risk difference of gastrointestinal hemorrhage

	Prapranolol group		Control group		Risk difference and its 95 % CI (%)
	Total	Bled	Total	Bled	
Primary prevention					
Pascal (1984)	34	1	35	9	-23 [-38, -7]
Mills (1987)	38	19	43	33	-27 [-47, -6]
Pascal (1987)	118	20	112	30	-10 [-20, 1]
Italian (1988)	85	16	89	27	-12 [-24, 1]
Strauss (1988)	20	4	16	4	-5 [-33, 23]
Colman (1990)	23	8	25	2	27 [5, 49]
Andreani (1990)	43	2	41	13	-27 [-43,-11]
Conn (1991)	51	4	51	14	-20 [-34, -5]
Prova (1991)	68	23	72	19	7 [-8, 23]
Subtotal	480	97	484	151	-11 [-21, -1]
Overall effect			*Z*=-2.15	*P*=0.03	
Secondary prevention					
Burroughs (1983)	26	14	22	13	-5 [-33, 23]
Lebrec (1984)	38	6	36	23	-48 [-68,-29]
Cerbelaud (1986)	42	17	42	33	-38 [-57,-19]
Villeneuve (1986)	42	32	37	30	-5 [-23, 13]
Queuniet (1987)	51	29	48	31	-8 [-27, 11]
Marbet (1988)	10	2	10	9	-70 [-101,-39]
Colombo (1989)	32	8	30	14	-22 [-45, 2]
Sheen (1989)	18	8	18	15	-39 [-68,-10]
Garden (1990)	38	20	43	36	-31 [-50,-12]
Colman (1990)	26	9	26	13	-15 [-42, 11]
Perez-Ayuso (1991)	26	16	28	24	-24 [-47, -1]
Calès (1999)	102	3	104	4	-1 [-6, 4]
Subtotal	451	164	444	245	-25 [-39,-10]
Overall effect			*Z*=-3.34	*P*=0.0008	
All trials					
Total	931	261	928	396	-18 [-25, -10]
Overall effect			*Z*=-4.38	*P*=0.00001	

In the 20 trials, among the 652 patients with upper gastrointestinal tract hemorrhage, 261 were treated with propranolol, and 396 were treated with placebo or not treated. The overall weighted bleeding rate was 31 % for propranolol and 48 % for controls. The pooled risk difference was -18 % [95 % CI, -25 %, -10 %], and the reduction had statistical significance (Z=-4.38, P<0.001, Table 1).

A total of 440 patients died, 188 in propranolol groups and 252 in control groups. The overall weighted bleeding rate was 17 % after propranolol treatment and 24 % after placebo treatment. The pooled risk difference was -7 % [95 % CI, -12 %, -3 %], and the reduction due to propranolol also was statistically significant (Z=-3.44, P<0.001, Table 2).

In ten trials, the overall weighted rate of death due to bleeding was 6 % in propranolol groups and 12 % in controls. The pooled risk difference was -5 % [95 % CI, -9 %, -2 %] (Z=-3.12, P=0.002).

Table 2 Point estimates and 95 % CIs of the risk difference of death

	Prapranolol group		Control group		Risk difference and its 95 % CI (%)
	Total	Death	Total	Death	
Primary prevention					
Pascal (1984)	34	1	35	13	-34 [-51, -17]
Mills (1987)	38	15	43	19	-5 [-26, 17]
Pascal (1987)	118	25	112	40	-15 [-26, -3]
Italian (1988)	85	30	89	22	11 [-3, 24]
Strauss (1988)	20	7	16	7	-9 [-41, 23]
Colman (1990)	23	6	25	7	-2 [-27, 23]
Andreani (1990)	43	13	41	18	-14 [-34, 7]
Conn (1991)	51	8	51	11	-6 [-21, 9]
Prova (1991)	68	7	72	14	-9 [-21, 3]
Subtotal	480	112	484	151	-9 [-18, -1]
Overall effect			*Z*=-2.11	*P*=0.03	
Secondary prevention					
Burroughs (1983)	26	4	22	5	-7 [-30, 15]
Lebrec (1984)	38	3	36	8	-14 [-30, 2]
Cerbelaud (1986)	42	5	42	12	-17 [-33, 0]
Villeneuve (1986)	42	19	37	14	7 [-14, 29]
Queuniet (1987)	51	12	48	13	-4 [-21, 14]
Marbet (1988)	10	1	10	3	-20 [-54, 14]
Colombo (1989)	32	4	30	7	-11 [-30, 8]
Sheen (1989)	18	0	18	2	-11 [-28, 6]
Garden (1990)	38	14	43	19	-7 [-29, 14]
Colman (1990)	26	1	26	1	0 [-10, 10]
Perez-Ayuso (1991)	26	4	28	7	-10 [-31, 12]
Calès (1999)	102	9	104	10	-1 [-9, 7]
Subtotal	451	76	444	101	-5 [-9, -1]
Overall effect			*Z*=-2.26	*P*=0.02	
All trials					
Total	931	188	928	252	-7 [-12, -3]
Overall effect			*Z*=-3.44	*P*=0.0006	

Primary prevention

There were 964 patients in the nine primary prevention trials. Of the total 480 patients treated with propranolol, 97 patients bled from upper gastrointestinal tract, the overall weighted rate was 20 %. And 112 patients died, the overall weighted rate was 22 %. In the control groups (484 patients), the overall weighted rate of bleeding was 31 % (151 patients), and that of death was 31 % (151 patients).

The pooled risk difference of bleeding was -11 % [95 %CI, -21 %, -1 %], and that of death was -9 % [95 % CI, -18 %, -1 %]. Both of the reduction due to propranolol had statistical

significance (Table 1, Table 2).

Death due to bleeding was reported in 5 primary prevention trials, the overall weighted rate was 6 % in propranolol groups and 10 % in controls. The pooled risk difference was -4 % [95 % CI, -8 %, 0 %] (Z=-2.06, P=0.04).

Secondary prevention

Among the 895 patients in the twelve secondary prevention trials, 451 were treated with propranolol and 444 were treated with placebo.

The number of patients with bleeding was 164 in propranolol groups and 245 in control groups, the overall weighted rate was 39 % and 63 % respectively. The pooled risk difference of hemorrhage was -25 % [95 % CI, -39 %, -10 %], which had statistical significance (Z=-3.34, P<0.001, Table 1).

In all secondary prevention trials, the total number of patients died after propranolol treatment was 76, and 101 in controls. The overall weighted rate of death was 13 % and 20 % respectively. The pooled risk difference of death was -5 % [95% CI, -9 %, -1 %], and the reduction was statistically significant (Z=-2.26, P=0.02, Table 2).

In 5 recurrent prevention trials, the overall weighted rate of death due to bleeding was 6 % after propranolol treatment and 15 % in controls. The pooled risk difference was -8 % [95% CI, -15 %, -2 %] (Z=-2.53, P=0.01).

DISCUSSION

Propranolol reduces portal pressure, portal blood flow, and superior portosystemic collateral blood flow, so it can reduce the variceal pressure to prevent upper gastrointestinal hemorrhage[1-3]. However, reduction of the risk of gastrointestinal bleeding could not be replicated in some trials[7, 19, 21]. In the present meta analysis, we reviewed 20 randomized clinical trials to assess the efficacy of propranolol on gastrointestinal hemorrhage. The overall results showed that propranolol significantly reduced the risk of upper gastrointestinal tract bleeding, with a same effect on survival.

The beneficial effect of propranolol on both first and recurrent gastrointestinal hemorrhage was observed in all but six of the trials. The average rate of gastrointestinal hemorrhage was 28 % in patients treated with propranolol, but 43 % in controls, suggesting that this interventional therapy is highly effective on prevention of upper gastrointestinal tract bleeding. The results also demonstrated the efficacy of propranolol on preventing the first episode or recurrence of upper gastrointestinal tract bleeding in patients with cirrhosis. In the six trials, propranolol used to prevent variceal bleeding was proved to be ineffective, four were published in full form[7,10,19,21], and two in abstract form[25, 26].

The results of this meta analysis showed that propranolol significantly affected survival in all trials, primary prevention trials, or secondary trials. The average mortality was 20 % in patients treated with propranolol, but 27 % in controls. The reduction in total mortality was consistent with a limited effect on death due to bleeding. Other causes of death, including liver failure, sepsis, and the development of hepatocellular carcinoma, were not affected by propranolol.

Although the beta-blockade effect of propranolol can decrease hepatic blood flow, which may in turn induce deterioration of liver function in cirrhotic patients, but hepatic decompensation has been rarely encountered in patients treated with propranolol. In addition, other adverse effects of propranolol such as hypotension (3.6 %), heart failure (2.2 %), arrhythmia (1.4 %), bronchial spasm (2.7 %), dizziness (2.0 %), asthenia (3.4 %) etc were rarely encountered.

Endoscopic sclerotherapy is a conventional treatment for reducing the risk of recurrent bleeding, and long-term survival may also improve[28-33]. Another meta analysis which we conducted showed that the average recurrent bleeding rate was 42 % after endoscopic sclerotherapy, but was only 36 % in propranolol groups, and 55 % in control group in our present meta analysis. A randomized clinical trial suggested that the efficacy of combined sclerotherapy and propranolol on the primary prevention of hemorrhage in cirrhotic patients with varices was the same as propranolol alone[34]. In other words, endoscopic sclerotherapy did not consistently improve survival. Sclerotherapy, like propranolol, is associated with a low incidence of side-effects, but side effects such as esophageal perforation, may be life-threatening. The technique also is more time demanding on both physicians and patients.

In conclusion, the results of this meta analysis of the existing controlled trials show that propranolol is an effective means of reducing both the incidence of bleeding from upper gastrointestinal tract and the total mortality, and has the advantage of being safe and cost-effective. The combined data indicate that propranolol reduces the risk of bleeding or rebleeding by about 20 %, in both primary and secondary prevention and it also reduces mortality. The primary prevention trials, which included patients with obvious varices at high risk of bleeding, clearly show a beneficial effect. Based upon the analysis we would recommend a long-term treatment of gastrointestinal hemorrhage with propranolol. However, for many patients with portal hypertension without obvious varices, large prospective multicenter trials are indicated to determine the preventive benefit of propranolol. Further comparative trials of propranolol versus sclerotherapy are required to identify which is superior for secondary prevention of gastrointestinal hemorrhage.

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