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PROPHYLACTIC β-BLOCKER THERAPY: CLINICAL IMPLICATIONS OF AN AGGREGATE ANALYSIS

Poynard T, Calès P, Pasta L, Ideo G, Pascal JP, Pagliaro L, Lebrec D, et al. Beta-adrenergic-antagonist drugs in the prevention of gastrointestinal bleeding in patients with cirrhosis and esophageal varices. N Engl J Med 1991;324:1532-1538.

ABSTRACT

Background. **The value of beta-adrenergic-antagonist drug therapy for the prevention of initial episodes of gastrointestinal bleeding in patients with cirrhosis and esophageal varices is uncertain, both positive and negative study results having been reported.**

Methods. **In this study, we analyzed data on individual patients from four randomized, controlled trials to assess the efficacy of this treatment. Of the 589 patients studied, 286 received a beta-adrenergic-antagonist drug (propranolol in 203 and nadolol in 83) and 303 received placebo.**

Results. **After two years, the mean (± SE) percentage of patients who had had no upper gastrointestinal bleeding was 78 ± 3 percent in the beta-adrenergic-antagonist treatment group and 65 ± 3 percent in the control group (P = 0.002). The percentage of patients without fatal bleeding was 90 ± 2 percent in the treatment group and 82 ± 3 percent in the control group (P = 0.01). The percentage of patients surviving after two years was 71 ± 3 percent in the treatment group and 68 ± 3 percent in the control group (P = 0.34). After age and severity of cirrhosis were taken into account, the survival rate was better in the treatment group (P = 0.09). The percentage of surviving patients who had had no bleeding after two years was 62 ± 3 percent in the treatment group and 53 ± 3 percent in the control group (P = 0.04). Both propranolol and nadolol prevented a first episode of bleeding. Severe cirrhosis and especially the presence of ascites were associated with bleeding (P < 0.001) and death (P < 0.001) in both groups. The efficacy of beta-adrenergic-antagonist therapy in the prevention of bleeding (P < 0.001) and of fatal bleeding (P = 0.004) and in the prevention of bleeding or death (P = 0.005) was the same after adjustment for cause and severity of cirrhosis, ascites, and size of varices.**

Conclusions. **Propranolol and nadolol are effective in preventing first bleeding and reducing the mortality rate associated with gastrointestinal bleeding in patients with cirrhosis, regardless of severity.**

COMMENTS

The high mortality rate of an initial variceal bleed in a patient with cirrhosis and portal hypertension makes primary preventive treatment desirable (1). Although β-adrenergic antagonist drugs have been shown to reduce portal pressure by reducing splanchnic blood flow (2), the results from the published trials (3-7) and abstract reports (8-10) of randomized clinical trials using this treatment as the primary prevention against esophageal variceal bleeding and related death have been inconsistent, possibly as a result of differences in study populations.

In an attempt to resolve the inconsistency, two groups performed a meta-analysis of the published trials (11, 12) and concluded that β-adrenergic blockade was efficacious in preventing esophageal bleeding. However, "classical meta-analysis" may be limited by clinical heterogeneity among the studies, and, more importantly, this technique may be unable to identify subgroups in which the proposed therapy is highly effective, ineffective or possibly even harmful.

Poynard and colleagues ventured a step beyond "classical" meta-analysis (which uses summary-level data) by combining the original, individual-level data from four (we presume the most rigorous) of the available studies. This innovative strategy provides an opportunity to adjust for clinically important differences among study populations using multivariate analysis and allows for investigation of a treatment effect in a greater number of subgroups than is possible with classical meta-analysis. For example, in contrast to the previous two meta-analyses addressing these studies, Poynard et al.'s individual-level data demonstrated a trend toward improved overall survival with β-blocker therapy when adjusted for age and disease severity ($p < 0.09$). Furthermore, although the authors did not report cause-specific deaths, the data from their Table 1 suggest that β-blockers decreased the risk of death from bleeding (7.3% vs. 14.2%; unadjusted relative risk = 0.52, 95% confidence interval = 0.32-0.85).

Although the conclusions appear to answer the question of overall effectiveness of β-blockers in preventing an initial upper gastrointestinal hemorrhage, the specific clinical application of β-blockers in this setting remains ambiguous. Which clinical variables (either individually or in combination) predict the best (or no) response to β-blockers is not clear from this study.

On the basis of Kaplan-Meier life table analysis for

patients free of bleeding, the authors concluded that β-blockers were effective in patients with and without ascites and in patients with severe and mild-to-moderate liver disease (i.e., virtually all patients benefited). The authors did state, however, that patients without ascites and patients with severe liver disease derived greater benefit from treatment. Although the Kaplan-Meier analysis is a very sensitive method for detecting therapeutic benefit over time and under changing conditions, it may not have great clinical applicability for selecting patients who would most benefit from therapy regarding bleeding. Reanalysis of the data in Table 4 of the study using unadjusted relative risks is provided in our Table 1. If the relative risk of bleeding is calculated over the 2-yr study period (rather than the percentage of patients free of bleeding using the Kaplan-Meier method), treatment was more effective among patients without ascites and among patients with poor liver function as defined by a Child-Pugh score greater than or equal to 8. The protective efficacies (1 = relative risk) of β-blockers were 52% and 44% for these subgroups, respectively. No significant decrease in the relative risk of bleeding was observed with treatment in either those patients with good liver function (Child-Pugh score <8) or those patients with ascites, although the power to detect clinically important risk reductions may have been limited. Although it may initially seem contradictory that β-blockers should prevent initial bleeds in patients with severe disease (Child-Pugh score) but not in patients with ascites, the five parameters used to calculate the Child-Pugh score do not always change in concert. Furthermore, β-blockers may decrease portal pressure to the same magnitude in patients with and without ascites but may not reduce the pressure gradient across the hepatic sinusoidal bed in ascitic patients low enough (the absolute threshold requirement is 12 mm Hg) to prevent gastrointestinal hemorrhage caused by portal hypertension (13). A lack of efficacy in patients with ascites has been noted previously (4) and assumes greater importance because patients with intractable or tense ascites resistant to therapy were excluded from three of the four studies included in the Poynard et al. study.

Although an appropriate "intention-to-treat" analysis was used by the authors, this method of analysis is a more rigorous test for treatment effectiveness and it can sometimes mask or underestimate therapeutic efficacy. Because noncompliance was an independent variable associated with bleeding, it is possible that different results would have been obtained using an analysis-by-treatment-received method.

Perhaps the most important issue concerns the generalizability of the results. All study patients had clinical and/or histological evidence of cirrhosis, esophageal varices and no previous upper gastrointestinal bleeding. Exclusions, which reduced eligible participants by approximately 25%, included contraindications to β-blockers (for conditions that often coexist with cirrhosis); HCC; intractable ascites, encephalopathy or both; and severe cirrhosis as defined by the Child-Pugh score. Finally, withdrawals caused by adverse effects of β-blocker therapy must be considered. In one trial (4), this accounted for the withdrawal of 14% of randomized subjects. Although β-blockers are generally considered to be well tolerated, relatively inexpensive and without major side effects, at least one preliminary report has found increased bleeding in propranolol-treated patients (9). In addition, the long-term effects of suppressing the elevated catecholamines present in cirrhosis are unknown. One possible adverse effect of such suppression might be an increase in the irreversible loss of nitrogen (14). Considering these issues, it appears premature to recommend either widespread endoscopic screening or the general use of β-blockers as prophylaxis against an initial episode of esophageal variceal bleeding without improved patient selection. Such information should be obtainable from the data collected by Poynard et al. and, it is hoped, will be forthcoming in more detailed reports.

Finally, the importance of combining individual-level data from multiple studies needs to be emphasized. As outlined above, and as Poynard and colleagues have recognized, this approach may be the optimal method for effectiveness research and assessment of clinical outcomes (15). Perhaps it is time to consider a national registry for individual-level data obtained from randomized clinical trials that would preclude the necessity of performing meta-analyses with their potential limitations for clarifying clinical applicability. Such a registry could be monitored through local human investigation committees; in addition, a registry would likely enhance the validity and precision regarding the efficacy of both new and old therapeutic agents.

TABLE 1.

Category of patients	No. with bleeding/No. of patients		Relative risk (95% CI)	No. needed to be treated[a]
	Treatment	Control		
No ascites	16/134	36/146	0.48 (0.28-0.83)[b]	8
Ascites	33/149	48/153	0.71 (0.48-1.03)	–
CPS greater than or equal to 8	26/143	45/139	0.56 (0.37-0.86)	7
CPS less than 8	22/140	37/163	0.69 (0.43-1.11)	–

CI = confidence interval; CPS = Child-Pugh score.
[a]Calculated only if 95% CI excluded one.
[b]Numbers in parentheses = range.

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TREATMENT OF REFRACTORY ASCITES: IS DIALYTIC ULTRAFILTRATION BETTER THAN PARACENTESIS?

Lai KN, Li P, Law E, Swaminathan R, Nicholls MG. Large-volume paracentesis versus dialytic ultrafiltration in the treatment of cirrhotic ascites. Q J Med 1991;78:33-41.

ABSTRACT

We compared the clinical efficacy and safety of large-volume paracentesis and dialytic ultrafiltration in the treatment of refractory ascites in cirrhotic patients. A group of cirrhotic subjects (age 49-80 years) were randomly allocated to either continuous paracentesis (1-1.5 l/hour) or dialytic ultrafiltration until disappearance of ascites. Each patient was maintained on bed rest, fluid restriction (1 l/day) and a low (25 mmol/day) sodium diet for 14 days. Five patients (three in the paracentesis group and two in dialytic ultrafiltration group) developed massive ascites 3-5 months later, and received the crossover treatment. The average volume of fluid removed was similar in the two groups (4.70 ± 1.47 l for dialytic ultrafiltration *versus* 4.69 ± 1.84 l for paracentesis), but the treatment period was significantly shorter with dialytic ultrafiltration. The plasma creatinine significantly increased three days after paracentesis but did not increase in patients treated with dialytic ultrafiltration. There was an initial fall in mean arterial pressure during the first two hours of either treatment; a further fall in blood pressure was observed with paracentesis but not with dialytic ultrafiltration. Pretreatment plasma renin activity was elevated, but was not altered by either treatment. Plasma atrial natriuretic peptide levels were in the high-normal range before treatment. Paracentesis was associated with a delayed fall in plasma atrial natriuretic peptide, while dialytic ultrafiltration induced a modest but significant rise. No complication was experienced with dialytic ultrafiltration in the two weeks following treatment, but four of the eight patients who underwent paracentesis had developed severe complications. Dialytic ultrafiltration of ascitic fluid is a safe procedure in cirrhotic patients. Large-volume paracentesis without intravenous colloid reinfusion causes complications and carries the potential risk of reducing the effective intravascular volume.

COMMENTS

Refractory ascites is one of the most feared complications of advanced cirrhosis. Ascites is severe, with great discomfort for the patient, who almost always has arterial hypotension, poor kidney function and hyponatremia. Diuretics are ineffective or not tolerated, and thus alternative treatments are required. The methods usually used to treat this condition are large-volume paracentesis and peritoneovenous shunt (1), but neither is completely safe nor satisfactory. In this study Lai et al. confirmed their previous results (2, 3) on the safety and efficacy of dialytic ultrafiltration (DUF).

In the 1970s a method of ascitic fluid filtration by Rhodiascit followed by intravenous reinfusion of the protein concentrate was used extensively in Europe (4). However, the incidence of untoward effects related to intravenous reinfusion, namely, disseminated intravascular coagulation, fever, sepsis and allergic reactions, limited clinical confidence in this technique. DUF is an innovation made possible by the development of hemofilters that provide a sterile filtrate. The reinfusion of the concentrated ascites intraperitoneally instead of intravenously frees the treatment from any important risk. It also prevents disorders related to hypovolemia, presumably because raising the concentration of proteins of the peritoneal fluid leads to retrodiffusion of albumin into the vascular compartment (5). Therefore expansion