Is carvedilol better than propranolol in portal hypertension?

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Background

Liver cirrhosis is a leading cause of death worldwide. Portal hypertension remains as a major complication of liver cirrhosis. Hepatic venous pressure gradient (HVPG) measurement is the best available method to evaluate the presence and severity of portal hypertension (1). Beta blockers have been shown to reduce HVPG and thus reduce further complications, such as ascites and hepatorenal syndrome (1). Traditional non-selective beta blockers (NSBB) such as propranolol, or endoscopic variceal ligation (EVL) were considered the gold standard in the prevention of first variceal haemorrhage arising from raised portal pressures (Baveno V) (2).

Carvedilol versus propranolol

Carvedilol non-inferior to propranolol

Traditional NSBB such as propranolol reduces portal pressure by their Beta 1 blockade (which decrease cardiac output) and Beta 2 blockage (which constrict the splanchnic vessels). Carvedilol which blocks both alpha and beta blockers, is postulated to have better efficacy at lower HVPG than propranolol. For successful protection against gastrointestinal variceal bleeding, the portal pressure has to be decreased to less than 12 mmHg or by 20% of baseline values.

In their paper, Li *et al.* (BMJ 2016 Systemic review and meta-analysis of 12 RCTs), the authors analysed severe papers that compared carvedilol with propranolol looking at primary outcomes, which include (I) all-cause mortality; (II) bleeding related mortality; (III) upper gastrointestinal bleeding, as well as secondary outcomes, which include (I) HVPG reduction; (II) hemodynamic response rate; (III) post treatment MAP; (IV) adverse event. It was found that overall carvedilol may be more successful than propranolol or nebivolol in decreasing portal pressure and it may be as good as EVL in preventing variceal bleeding. However, the overall quality of evidence is low, as the number of patients included in many of the included trials is few (3).

In a randomised study comparing carvedilol with propranolol by Hobolth *et al.* at the end of the treatment period, HVPG had decreased by –19.3%±16.1% (P<0.01) in the carvedilol group and by –12.5%±16.7% (P<0.01) in the propranolol group with no significant difference between the two treatment groups (P=0.21) (4). The number of patients with a HVPG response 20% or to HVPG <12 mmHg after 90 days was not significantly different between the two groups: [13/21 (62%) in the carvedilol group versus 7/17 (41%) in the propranolol group, P=0.20] (4). In conclusion, this randomised comparison showed that the portal pressure effects of carvedilol and propranolol are at least equal after 90 days of treatment (4).

The above trial results were similar to the study by De *et al.* who followed 36 patients for 7 days and found no significant difference in HVPG using either carvedilol or propranolol (5).

In the study by Hobolth, the reduction in HVPG was not significant. This may be because the authors used a mean titrated dose of 14 mg carvedilol compared with 31 mg in the studies by Bañares *et al.* (4,6). The difference in dose of carvedilol may explain why there is a significant difference in HVPG between carvedilol and propranolol in another study by Bañares *et al.* In this study, the authors analysed the HVPG in 51 patients treated for 11 weeks and found that carvedilol caused a greater decrease in HVPG than propranolol (–19%±2% *vs.* –12%±2%; P<0.001). The proportion of patients achieving an HVPG reduction ≥20%

or ≤12 mm Hg was greater after carvedilol (54% *vs.* 23%; P<0.05) (6).

Carvedilol is more effective than traditional NSBB in reducing HVPG but has not been adequately compared head-to head to traditional NSBB in clinical trials (Baveno VI) (2).

Carvedilol better than propranolol

In a meta-analysis by Sinagra *et al.* looking at a few well described RCTs [led by Hoboth *et al.* (4), De *et al.* (5), Bañares *et al.* (6)], carvedilol reduces HVPG significantly than propranolol either after one single administration or in a more long term follow up from 1 week to 3 months (7).

Carvedilol is more effective than propranolol plus isosorbide 5 mononitrate (ISMN) in the reduction of HVPG. In addition, its systemic effects were similar to those of propranolol plus ISMN in a study by Lin *et al.* (8). However, in this study, nitrates may be a potential confounder.

Other investigators have performed trials which suggest that carvedilol is even better than propranolol. In a head to head trial comparing the two beta blockers, it was investigated by Abid *et al.* whether "It is time to replace propranolol with carvedilol for portal hypertension?". They found that carvedilol has proven to be 2–4 times more potent than propranolol as a beta-receptor. With regards to secondary prophylaxis of variceal bleeding, carvedilol has also been shown to be effective than propranolol (9).

Carvedilol versus EVL

It is safer to use pharmacological treatment methods such as carvedilol or NSBB are safer than EVL to treat portal hypertension as complications are often milder and subside after dose reduction or drug discontinuation (10). In a multicentre randomised control trial, Tripathi *et al.* showed that carvedilol has a significantly lower rate of first variceal bleeding in patients taking carvedilol 12.5 mg daily compared with EVL [10% versus 23%; relative hazard 0.41; 95% confidence interval 0.19–0.96 (P=0.04)], with no significant differences in overall mortality (35% versus 37%, P=0.71), and bleeding-related mortality (3% versus 1%, P=0.26) using intention-to-treat analysis (10).

Other benefits of carvedilol

NSSB has been proven to decrease the incidence of bleeding (primary prophylaxis) and rebleeding (secondary prophylaxis) from oesophageal varices. It has also been shown that they also prevent bleeding from portal hypertensive gastropathy and development of spontaneous bacterial peritonitis. Carvedilol may be useful in reducing HVPG in propranolol non-responders. In this study, 67 patients were categorized as propranolol non-responders out of 104 patients. Of these, 37 (56%) achieved hemodynamic response with carvedilol while the remaining 29 patients were treated with EVL (11). Specifically, they recommend using carvedilol at 6.25–12.5 mg/day, since higher dosage have resulted in further decrease of mean arterial pressure and heart rate without additional effect on HVPG (12). In addition, there have been several trials, including Capricorn study, have showed that carvedilol is beneficial in reducing cardiovascular mortality (13). It may be worthwhile to continue carvedilol in patients already on in for cardiac protection purposes.

Are there any downsides of using carvedilol?

Carvedilol can cause systemic hypotension and result in greater mortality in patients with decompensated cirrhosis.

Razon-Gonzalez *et al.* showed that Carvedilol is superior to propranolol in reducing HVPG (–8.36, 95% CI: –9.43 to –7.28, P<0.00001). However, reduction of MAP is significantly greater in carvedilol than in propranolol as well (–8.62, 95% CI: –9.63 to –7.61, P<0.0001) (11). In addition, risks of systemic hypotension are high in patients with decompensated liver cirrhosis (11). Hence, Carvedilol dose should be titrated slowly and not be increased in patient developing symptoms of hypotension or with SBP <90 mmHg or HR <50 bpm. Carvedilol is contraindicated in patient with marked bradycardia, sick sinus syndrome and heart block. Also contraindicated in patients with asthma, cautious in patients with insulin-dependent diabetes (14).

Take home messages: carvedilol carries a double edged sword with its alpha1 blocking abilities to cause systemic vasodilation. Systemic reviews and meta-analysis comparing acute head to head comparison of carvedilol and propranolol are difficult to perform because of the different doses of medications used (14). Nonetheless, overall taking into account all the evidence, carvedilol has been shown to be more effective than propranolol in reducing HVPG and hence preventing the complications of portal hypertension.

Specifically, in selected patients, e.g., propranolol non-responders or in patients at high cardiovascular risk, carvedilol may be more suitable than propranolol. However, dose titration of carvedilol should be done slowly and systemic blood pressure closely monitored. "*Each choice*

has a consequence. Each consequence has a destination." Joseph B. Wirthlin. When making the choice of using carvedilol over propranolol or EVL, we have to be cautious of adverse side effects of carvedilol, such as systemic hypotension and thus potential mortality especially in patients with decompensated liver cirrhosis.

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