Supplementary data 2: Study protocol

Use of beta-blockers in portal hypertension: Are there responders and non-responders?

Edmonton, 10th October 2021

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BACKGROUND

Parallel randomized trials serve to assess group differences, but cannot specifically assess individual responses [1]. The individual patient response cannot be directly observed as due to random assignment only one potential outcome will be observed, but the other will be a missing outcome.

Several randomized trials have shown that non-selective beta-blockers (NSBBs) improve several clinical outcomes [2]. In addition, longitudinal studies have shown that, as a group, those patients that achieve a >20% reduction in HVPG (or to levels <12 mmHg) have a much better prognosis than patients not achieving these hemodynamic targets [3,4]. It has been suggested that >50% of patients treated with conventional NSBBs (nadolol/propranolol) do not achieve these hemodynamic targets and are therefore referred to as "non-responders to NSBBs" [3]. This assumes that the response to NSBBs is heterogeneous among patients (some patients responding and some non-responding).

On this basis it has been suggested by some that portal pressure measurements (hepatic venous pressure gradient or HVPG) should be used to guide therapy with NSBBs as a way to personalized patient care improving the precision of NSBBs treatment [5]. However, after over 30 years of use of NSBBs for portal hypertension, only one low quality trial has compared HVPG-guided with non-HVPG guided therapy [6], whereas over 50 trials have assessed the efficacy of beta-blockers in different contexts of cirrhosis with portal hypertension [7].

In addition, recent data suggests that the consistency of HVPG measurements might be insufficient to reliably detect at the individual patient level relevant changes in portal pressure related to a drug intervention [8].

Recently, Cortes et al. in an elegant study [9] suggested that the heterogeneity in the effects of an intervention can be indirectly quantified from randomized parallel trials by assessing the variance in the outcome measurement in the experimental and control groups, and in the

intervention groups between baseline and outcome measurements. In that study, most interventions were not associated with heterogeneity of effects. Even more, variance in the outcome in the intervention groups was, in mean, lower than in the control groups. This has been also assessed in conditions such as Schizophrenia [10] and Depression [11], again suggesting little or no heterogeneity of treatment effects.

Since determining if NSBBs effect on portal pressure is heterogeneous in cirrhosis patients would have implications for personalized medicine, in the present study we aim at quantifying this heterogeneity by reviewing the results of randomized controlled trials in which HVPG was the primary outcome comparing NSBBs with placebo (or no intervention).

Furthermore, since carvedilol has been shown to increase the rate of "responders" as compared to nadolol or propranolol [12], we will also compare the heterogeneity in outcome HVPG in studies comparing carvedilol with propranolol or nadolol.

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meta-analysis: the haemodynamic effects of carvedilol compared with propranolol for portal hypertension in cirrhosis. Aliment Pharmacol Ther 2014;39(6):557–68.

SPECIFIC AIMS

1. To compare the variance between outcome HVPG in patients treated with beta-blockers (propranolol, nadolol, timolol or carvedilol) vs placebo. **MAIN COMPARISON**
2. To compare the variance between outcome HVPG between patients randomized to carvedilol vs propranolol/nadolol (TAKING INTO ACCOUNT THAT CARVEDILOL HAS BEEN SUGGESTED TO BE ASSOCIATED WITH GREATER PROPORTION OF RESPONDERS)
3. Since a few recent trials have compared the effects on portal pressure of statins vs placebo, and statins decrease portal pressure through a completely different mechanism than NSBBs (decreasing hepatic resistance) we will assess if the outcome variance is different between statins/placebo, and in the statins arm between baseline and outcome HVPG.

Note: there are several trials comparing Beta-blockers+nitrates with beta-blockers alone or with placebo. Nitrates are not used anymore, so these trials are of no interest now.

METHODS

Inclusion criteria for the studies

A. Placebo controlled trials comparing the effects on HVPG (portal pressure) of propranolol, nadolol or carvedilol with placebo. (We will add, in addition, the trial assessing timolol vs placebo, even if timolol is not currently used for the management of portal hypertension. The reason being that even if trials with timolol were negative on clinical endpoints, authors of those trials still tried to identify "responders".

B. Placebo controlled trials comparing the effect on HVPG of carvedilol and nadolol/propranolol

C. Placebo controlled trials evaluating the effects of statins on HVPG

Systematic search will be drafted with the help of University of Alberta librarian. Databases: Medline, EMBASE, Cochrane Library. Studies will be introduced in Covidence for screening (assessment for two evaluators required).

Concepts for the search:

1. Cirrhosis
2. HVPG
3. Propranolol, Nadolol, Carvedilol
4. RCTs

Data extraction (two parallel reviewers):

Study first author:
Year:
Id:

Intervention:
Control:

N Baseline intervention
N Baseline control

HVPG baseline intervention:
SD HVPG baseline intervention
SE HVPG baseline intervention (when reported instead of SD)
HVPG baseline control:
SD HVPG baseline control:
SE HVPG baseline control (when reported instead of SD)

N outcome intervention
N outcome control

HVPG outcome intervention:
SD HVPG outcome intervention:
SE HVPG outcome intervention (when reported instead of SD)

HVPG outcome control
SD HVPG outcome control
SE HVPG outcome control (when reported instead of SD)

Ancillary data:

Administration of beta-blockers (oral vs iv)
TIme between measurements
Distribution of etiology of cirrhosis

Severity of cirrhosis: Mean Child-Pugh if reported

Proportion of decompensated patients

Proportion of patients assessed at outcome (as compared to baseline)

Clinical context of the patients : I.e. patients after variceal hemorrhage, patients with compensated cirrhosis etc (free text to then codify)

Method of titration: free text to then codify (i.e. 25% reduction in HR, maximum tolerated dose, HVPG guided)

HVPG guided yes no (if titration of NSBBs was HVPG guided, one would expect less variability, since dose is adapted to achieve a maximum and therefore more homogeneous response. For example, Groszmann 1990 is HVPG guided, Villanueva 2019 is HVPG guided selection of propranolol or carvediol).

Data analysis:

Analysis will be done in R with the *metafor* package
The main outcome will be the VR (as in refs 7-11). In case of study to study heterogeneity ancillary variables will be used (if available) for moderator analysis to investigate heterogeneity.