Combining loop with thiazide diuretics for decompensated heart failure: the CLOROTIC trial

Introduction

- Acute heart failure (AHF) is the leading cause of hospitalization in older people and accounts for the highest healthcare costs in the USA and in Europe.
- The vast majority of patients admitted for AHF are treated primarily with intravenous loop diuretics
- The pathophysiology of diuretic resistance includes increased distal nephron sodium absorption in the case of (prolonged) loop diuretic administration.
- One approach to overcoming loop diuretic resistance is the addition of a thiazide diuretic to produce diuretic synergy via sequential nephron blockade

- As the role of combined diuretic therapy in AHF remains uncertain, we conducted the Safety and Efficacy of the Combination of Loop with Thiazide-type Diuretics in Patients with Decompensated Heart Failure (CLOROTIC) trial to evaluate whether the addition of hydrochlorothiazide (HCTZ) to intravenous furosemide is a safe and effective strategy for improving diuretic response in patients with AHF

Methods

- Design: multicentre, prospective, randomized, double-blind, placebo-controlled trial
- Study participants:
- 18 years of age or older, had a history of chronic HF (with no pre-specified inclusion criterion for HF aetiology and/or ejection fraction) and had been hospitalized within the previous 24 h for acute decompensated HF
- treatment with an oral loop diuretic, for at least 1 month
  - furosemide dose between 80 and 240 mg daily, or an equivalent dose
- Exclusion Criteria: unstable on admission (acute coronary syndrome, cardiogenic shock, and/or intensive care unit admission), treated with inotropic agents (other than digoxin) or with any thiazide diuretic during the month before admission
- Renal replacement therapy
- Hypokalemia and hyponatremia ($K<2.5$ mmol/L or $Na < 125$ mmol/L)

Treatment Groups

- Patients were randomly assigned, on a 1:1 ratio, to receive HCTZ or placebo for 5 days, supplied as oral tablets (doses were adjusted according to eGFR estimated using MDRD)
- Same HCTZ dose was used during treatment period (no up or down titration was allowed); dosing could only be adjusted based on GFR.
- Patients were admitted for at least 5 days, and were monitored until 90 days after discharge.

Endpoints

- Two coprimary endpoints: efficacy and safety
- Efficacy endpoints: body weight changes and patient-reported dyspnea. From baseline to 72h after randomization.
- Secondary endpoints: changes in body weight and patient-reported dyspnoea 96 h after randomization, diuretic response, hospital length of stay, mortality, and rehospitalizations at 30 and 90 days
  - Diuretic response: 24 h diuresis quantification, weight loss per 40 mg of furosemide (at 72 and at 96 h), net fluid loss (24 h diuresis) per milligram of furosemide and mean loop diuretic dose administered from time of study enrolment to 72 h.

- For the VAS, patients were asked to evaluate their perceived dyspnoea by marking a 10 cm vertical line, with the top labelled ‘I can’t breathe at all’ and the bottom labelled ‘I can breathe normally’. We scored the patients’ markings on a scale of 0–100 by measuring the distance in millimetres from the bottom of the line

Safety Endpoints

- changes in renal function and changes in electrolyte levels (sodium and potassium)
- increase in serum creatinine levels >26.5 μmoL/L or a decrease in eGFR higher than 50% compared with baseline
- Hypokalaemia and hyponatraemia were defined as potassium levels equal or lower than 2.5 mmoL/L and sodium levels equal or lower than 125 mmoL/L
- Hypotension was defined as a systolic blood pressure of <90 mmHg or any symptomatic drop in systolic blood pressure

Results

- A total of 6914 patients underwent screening, and after 230 patients were included (between October 2014 and October 2019 at 26 clinical sites in Spain)
- The patient population had a high burden of comorbidities and high-risk features, including a history of hospitalization for HF within the previous 12 months (138, 60% of the patients), moderate renal dysfunction (median eGFR, 43 mL/min/1.73 m_2), and elevated natriuretic peptide levels (median NT-proBNP level, 4672 pg/mL)
- The mean ejection fraction was 55% and 143 (65.3%) of patients had an ejection fraction of 50% or greater.

- Patients were more likely to lose weight in HCTZ group compared with placebo (-2.3 vs -1.5 kg)
- No significant difference were observed in patient-reported dyspnea
- At the time of discharge, the median change in weight from randomization was greater in the HCTZ group compared with placebo but this difference was not statistically significant (P = 0.261) .
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- Diuretic response: significantly greater 24 h diuresis (1775 vs. 1400 mL; P = 0.05) and weight loss for each 40 mg of furosemide (both at 72 and 96 h) (P < 0.001).
- no significant differences in net fluid loss per milligram of furosemide (787 vs. 719 mL; P = 0.306)
- The total mean loop diuretic dose administered from enrolment to 72 h was 375 mg in the placebo group and 340 mg in the HCTZ group (P = 0.145).
- The dose of loop diuretic was reduced in a significantly higher proportion of patients in the HCTZ group at the end of the study treatment period (34 vs 19)
- There was no significant difference in the likelihood of a switch to oral diuretics during the study treatment period and until hospital discharge [35 (33%) in the placebo group and 38 (36%) in the HCTZ group, P = 0.832]

- post-hoc exploratory analysis of congestion variables, finding that at 72 and 96 h after randomization patients assigned to HCTZ had fewer, peripheral edema, pleural effusion, and ascites compared with those assigned to placebo
- The median length of stay during the index hospitalization was 7 days and did not differ significantly across the treatment groups
- A total of 42 patients (18.3%) died and 83 (36.1%) were rehospitalized within the 90-day follow-up period, but there were no significant differences between groups in mortality or rehospitalizations

- A higher proportion of patients who received HCTZ met the prespecified safety endpoint of impaired renal function (53 (46.5%) compared with 20 (17.2%) patients in the placebo group ($P < 0.001$))
- The median increase in serum creatinine level at 5 days was 0.00 (10.6–18.6) μmoL/L with placebo and 15.9 (7.1–37.1) μmoL/L with HCTZ; $P < 0.001$
- There were no significant differences between these two treatment groups in the other safety endpoints, hyponatraemia, and hypokalaemia. However, in a post-hoc analysis using higher potassium cut-off points (≤3.5 and ≤3.0 mmoL/L), hypokalaemia was more frequent in those who received HCTZ.

- The median maximum decrease in serum potassium levels from baseline to hospital discharge was -0.36 (95% CI: -0.46 to -0.26) with placebo and -0.70 (95% CI: -0.81 to -0.60) with HCTZ, providing a significant difference of -0.33 (95% CI: -0.50 to -0.20)
- Decrease in sodium was not significant between groups.
- there were no differences in magnesium values at baseline or at discharge, and there were no cases of hypomagnesaemia.
- Serious cardiac events were similar in the two groups (11 vs. 8). Renal failure and hyperkalaemia were more frequent with placebo (5 vs. 2 and 2 vs. 0, respectively), but hyponatraemia was more frequent with HCTZ (1 vs. 3). No symptomatic hypotension was reported as a serious adverse event and the proportion of patients that presented asymptomatic hypotension (systolic blood pressure lower than 90 mmHg) was similar in both treatment groups (9-10%)

- There was a benefit for most of the primary or secondary endpoints, including changes in weight, urine output and metrics of diuretic response, although only weight differences and weight differences per mg of furosemide were statistically significant.
- No significant differences in patients' global assessment of symptoms using dyspnoea scales and this finding is consistent with those of other clinical trials
- Although worsening of renal function occurred more frequently with HCTZ, there was no short-term evidence of worse clinical outcomes between the two groups at 90 days.

- There is a substantial concern about the risk of adverse events with the use of thiazides combined with loop diuretics in patients with HF. This concern is mainly based on a retrospective observational analysis employing propensity matching, showing that the combination diuretic therapy with metolazone (the most widely used thiazide-like diuretic in the USA) was associated with an increased risk of hypokalaemia, hyponatraemia, worsening renal function, and mortality.In contrast, in this trial, we did not observe a significant risk of hyponatraemia, hypokalaemia, or mortality.

- There is an old belief that thiazides lack efficacy in patients with glomerular filtration rate <30 mL/min
- Nevertheless, more recent studies have shown that combined regimens are more potent than HCTZ or furosemide in monotherapy for increasing fractional excretions of sodium and chloride in patients with hypertension and Stage 4 or 5 chronic kidney disease
- There were no differences in the length of hospital stay despite a better diuretic response with HCTZ. This may be explained, in part, because all patients had to be admitted (and could not be discharged) during the 5-day randomized treatment period for close monitoring of adverse effects

- The strength of this trial is that eligibility criteria were chosen to select a cohort generalizable to the AHF population with diuretic resistance. The admission due to AHF decompensation despite being treated with 80 mg or more of loop diuretics and the low urinary natriuresis highly suggest this fact.
- This study has several limitations. First, recruitment did not reach the post size required by the protocol due to slow enrolment
- Second, four characteristics of the patients at baseline were unbalanced between the two treatment groups, including gender, systolic blood pressure, body mass index, and ischaemic cause of HF
- we observed a large relative but small absolute overall weight loss and, as there was no specific requirement for congestion at inclusion, maybe if more volume overloaded patients had been enrolled, we would have seen larger absolute reductions in weight
- Forth, the patients who participated in the trial had a history of chronic HF and required moderate-to-high doses of loop diuretics before admission Our findings may not be applicable to patients with newly diagnosed HF or those with more modest diuretic requirements.
- Finally, in the follow up visits, neither renal function nor electrolytes were monitored, so we cannot guarantee that the worsening of renal function is transient and associated with a good diuretic response

- In conclusion, adding oral HCTZ to intravenous furosemide is an adequate strategy to improve diuretic response in patients with acute decompensated HF.

- اضافه کردن هیدروکلروتیازید خوراکی به فورزماید تزریقی استراتژی مناسبی برای بهبود پاسخ به دیورتیک در بیماران نارسایی حاد قلبی جبران نشده می باشد.