

# Furosemide Resistance in Heart Failure Patients

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### Question

Is there a protocol for administering high-dose furosemide with hypertonic saline solution to overcome diuretic resistance in heart failure patients?

Diuretics are considered first-line treatment in acute congestive heart failure (CHF), but resistance to these medications is common, particularly in long-term therapy. A variety of approaches can help overcome this resistance, including the addition of hypertonic saline solution (HSS) to the therapeutic regimen. Several studies have examined the efficacy of this strategy.

In a randomized, single-blind study, 60 patients with refractory, advanced CHF were randomized into 2 groups.<sup>[1]</sup> The first group received intravenous infusions of furosemide (500-1000 mg) plus 150 mL of HSS (1.4%-4.6% NaCl) twice daily in 30-minute periods. The second group received only an intravenous bolus of furosemide (500-1000 mg) twice daily. All patients also received KCl (20-40 mEq) to prevent hypokalemia.

Both groups experienced a significant increase in daily diuresis and serum uric acid, along with lower potassium levels, body weight, and blood pressure. The group receiving HSS also had increases in natriuresis and serum sodium, whereas the furosemide-only group experienced higher serum creatinine levels and longer hospitalizations.

In a 6- to 12-month follow-up, no patients from the HSS group had been readmitted to the hospital, and they all maintained their heart failure classification. Twelve patients in the furosemide-only group were readmitted at a higher heart failure classification. The authors concluded that furosemide plus HSS produces an improvement in hemodynamic and clinical parameters, reduces hospital time, and maintains obtained results, compared with high-dose furosemide alone.

Licata and colleagues<sup>[2]</sup> also conducted a single-blind study of 107 patients with CHF that was unresponsive to high doses of oral furosemide, as well as to angiotensin-converting enzyme (ACE) inhibitors, digitalis, and nitrates. Patients were randomized into 2 groups to compare the same treatment options as those in the previously mentioned study.

Both groups experienced a significant increase in diuresis and natriuresis, but results were more significant in the group receiving HSS. Serum sodium levels increased in the

HSS group and decreased in the furosemide-only group. Potassium levels, body weight, and blood pressure decreased significantly in both groups, while uric acid increased in both. Creatinine increased in the furosemide-only group.

Finally, a randomized, double-blind study examined 84 patients with refractory class IV CHF.<sup>[3]</sup> One group received the furosemide plus HSS therapy described above, while the other received torsemide 200 mg twice daily plus HSS. Both groups experienced a significant increase in daily diuresis and natriuresis, and a decrease in body weight and blood pressure. There was no difference in serum potassium or sodium. The authors concluded that torsemide is equivalent to furosemide in the treatment of refractory CHF.

The results of these pilot studies offer clinicians a novel approach to overcoming furosemide resistance in heart failure. However, these results should be confirmed in larger, randomized, double-blind studies.

## References

1. Paterna S, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail.* 2000;2:305-313.
2. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J.* 2003;145:459-466.
3. Paterna S, Fasullo S, Di Pasquale P. High-dose torsemide is equivalent to high-dose furosemide with hypertonic saline in the treatment of refractory congestive heart failure. *Clin Drug Investig.* 2005;25:165-173.

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