TITLE: Improving a service: subcutaneous furosemide in advanced heart failure.

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ABSTRACT

Objectives: In severe heart disease, parenteral administration of loop diuretic is often needed. We present clinical outcomes from episodes of care using subcutaneous continuous infusion of furosemide (CSCI-furosemide).

Methods: Retrospective review of service improvement data. The heart failure nurse specialist, supported by the heart failure-palliative care multi-disciplinary team, works with the community or hospice staff who administer the CSCI-furosemide. Data collected for consecutive patients receiving CSCI-furosemide included: age, sex, New York Heart Association (NYHA) class, preferred place of care, goal of treatment, infusion-site reactions, and signs and symptoms of fluid retention (including weight and self-reported breathlessness).

Results: 116 people (men 86 [66%]; mean age 79 years, 49 to 97; NYHA class 3 [36/116, 31%] or 4 heart failure [80/116, 69%]) received 130 episodes of CSCI-furosemide (average duration 10 days, 1 to 49), over half in the patient's own home/care home (80/129,; 61%) aiming to prevent hospital admission. 40/129 (31%) were managed in the hospice, and 9 (7.0%) in a community hospital. Average daily furosemide dose was 125 mg (40 to 300mg). The goal of treatment was achieved in (119/130, 91.5%) episodes.

The median reduction in weight was 4kg (interquartiles -7 kg to -2 kgs, -22 to +9 kgs). Self-reported breathlessness reduced from 8.2 (+/-1.9) to 5.2 (+/-1.8). Adverse events occurred in 31/130 (24%) episodes; all but 4/130 (3%, localised skin infection) were mild.

Conclusions: These preliminary data indicate that CSCI-furosemide is safe and effective for people with severe heart failure. An adequately powered randomised controlled trial is indicated.

KEY WORDS

Subcutaneous infusion; diuretic; furosemide; heart failure; palliative; service improvement

INTRODUCTION

Despite effective heart failure treatments and a reduced 10-year mortality [1], progression to advanced disease remains a cause of poor quality of life.[2] Congestive symptoms are a hallmark of heart failure, often needing parenteral loop diuretic, usually intravenous (IV) as a hospital in-patient.[3] In advanced disease, the focus shifts to symptom control and quality of life. For many, this means care at home where possible. Hospital admission drives the considerable health service costs,[4] and which for older people with chronic health conditions may also worsen frailty, sarcopenia, and cause nosocomial infections, contributing to functional decline. [5,6] This potential vicious cycle jeopardises independent living, and may mean death in hospital by default.

Community administered parenteral diuretics, either IV where community services exist, or subcutaneous is a possible solution.[7] A British Heart Foundation (BHF) pilot of community IV furosemide (n=126) found preliminary evidence of safety, benefit and cost-effectiveness.[8] A retrospective case-review of 43 episodes of continuous subcutaneous infusion of furosemide (CSCI-furosemide) in 32 people with advanced heart failure showed promising weight loss, and support for patient-preferred place of care.[9] The NICE chronic heart failure guideline,[3] highlighted subcutaneous diuretic administration as a research priority area. Since then, a nearly 100% bioavailability of subcutaneous furosemide has been demonstrated [10] and a pilot randomised controlled trial of subcutaneous versus IV has shown equivalent weight loss and diuresis.[10] As there are still relatively few data to inform clinical practice, we continued our CSCI-furosemide service improvement routine data collection,[9] and report findings from this larger cohort regarding fluid balance and management goals.

METHODS

This retrospective review of anonymised service improvement initiative data is reported according to SQUIRE.[11] Ethics approval was not required. Institutional approval was obtained.

Consecutive patients from a regional heart failure-palliative care multi-disciplinary service (heart failure nurses, palliative physician, cardiologists) were eligible for CSCI-furosemide if they; i) had optimised heart failure management, ii) required parenteral diuretic, iii) had a preferred place of care as home, hospice or care home, iv) had sufficient community support (informal and clinical). Patients received CSCI-furosemide according to institutionally-approved guidance, had contemporaneous data collected routinely using an anonymised proforma. No formal service improvement framework was used, but national heart failure treatment guidance was followed.[3]

The service is delivered by the heart failure nurse specialist working with general practitioners and community nurses, who administer the CSCI-furosemide; all having access to cardiologist advice. Furosemide for IV injection was used, diluted if needed with 0.9% saline, and infused over 24 hours using a subcutaneous syringe driver. The starting dose was estimated as the previous 24 hour oral dose: e.g. if the patient was taking 120mg/24 hours oral, the CSCI prescription was120mg/24 hours.

Data were collected by the usual care clinician and combined for Cohort A (October 2006 to July 2009, previously published, fluid overload symptoms and signs not collected),[9] and Cohort B (until July 2019, symptoms and signs collected). The service continued to gain a larger sample size, and record impact on signs and symptoms.

Clinical-demographic characteristics were recorded (age, sex, New York Heart Association (NYHA) class, place of care, preferred place of care, signs and symptoms [cohort B]) and treatment characteristics (dose, number of treatment days, adverse effects). Goals of care were noted: i) at home/care home wishing to prevent hospital admission; ii) in hospital, aim to facilitate discharge despite continued need for parenteral diuretics, iii) in hospice, aiming to stabilise heart failure, iv) in hospice, aiming to prevent terminal pulmonary oedema. Signs of fluid retention included jugular venous pressure (JVP) height, pulse, blood pressure, chest crackles and peripheral oedema were categorised as: i) JVP - not visible, <3 cm, >3 cm; ii) chest crackles - clear, basal, whole chest; iii) oedema -none, mild (below knee), moderate (above knee), severe (truncal/ascites). Patient-reported breathlessness used a 0 to 10 rating scale of "breathlessness now" (0 = no breathlessness; 10 = worst imaginable breathlessness). Site reactions categories were; infection (antibiotics prescribed, cellulitis), mild (erythema, bleeding, sore, swelling, trauma), practical (dislodged, leaking), or not described. We assumed clinical entry more likely for adverse events, with details if serious, so: i) where "No" was ticked, but there <u>was</u> descriptive text, we counted as "Yes" and categorised according to the description; ii) missing responses were counted as "No"; iii) where "Yes" was ticked but with no details, we assumed a mild reaction.

Descriptive statistics are tabulated. In this clinical dataset, there are missing data; the denominator represents the number of episodes for which the item was recorded. Assumptions were made for i) adverse events as above; ii) oedema - the most severe response was counted, iii) place and goal of care discrepancies agreed (MJ, EB) (e.g. place = "home", goal = "in hospital, aim of home discharge"; counted as "hospital"). With mutually exclusive options, data were treated as missing.

RESULTS

116 people with chronic advanced heart failure (men 86 [66.2%], mean age 79 years; standard deviation [SD] 10; range 49 to 97, NYHA class 3 [36/116, 31%] or 4 [80/116, 69%]) received 130 episodes of CSCI-furosemide (cohort A = 43, cohort B = 87) (see Online Table 1 for details).

Most episodes occurred in the patient's home or care home (80/129; 61%). A further 40/129 (31%) were in the hospice, and 9 (7%) in a community hospital.

The median duration was 10 days (interquartile range [IQR] 6 to 14, range 1 to 49). Mean daily starting dose was 125 mg and 137 mg at the end (range 40 to 300mg). The injection site was changed on average once *per* episode.

The goal of treatment was achieved in nearly all (119/130; 91.5%).

Signs of fluid overload (Table 1) showed: JVP > 3 cms in two-thirds, most had additional chest sounds, and over half had severe peripheral oedema. Self-reported breathlessness at baseline was severe (mean 8.2; SD 1.9).

End-of-episode data entry for signs and symptoms was less complete; some clinicians felt the measures were too burdensome, or they had insufficient time. However, anecdotal comment was that CSCI-furosemide was helpful. Median weight reduction was —4kg (IQR—7 kg to —2 kgs, range —22 to +9 kgs); 8/36 (22%) had a JVP > 3cm; 18/41 (44%) had chest crackles/wheeze and 4/50 (8%) had severe peripheral oedema. Self-reported breathlessness reduced (mean 5.2; SD 1.8). Pulse and blood pressure were stable.

Adverse events in 31/130 (24%) episodes were mostly mild (25/130; 19%) or practical problems (6/130; 5%). A few, 4/130 (3%), had localised site infections.

Table 1. Measures at baseline and end of episode

	Baseline	**End of episode (or last recorded)**	**Change**
Goal achieved			
Yes		119 (91.5%)	
No		11 (8.5%)	
Total (n)		130	
Signs and Symptoms			
JVP			
1= not visible	12 (18.5%)	13 (36.1%)	
2= <3cm	10 (15.4%)	15 (41.7%)	
3= >3cm	43 (66.2%)	8 (22.2%)	
Total (n)	65	36	
Pulse (beats per minute) (mean; SD)	79.0 +/- 15.0	77.0 +/- 4.0	−2.0 +/-15.5
Systolic BP (mmHg) (mean; SD)	111.0 +/- 33.0	112.0 +/- 30.0	1.0 +/- 44.6
Diastolic BP (mmHg) (mean; SD)	64.0 +/- 15.0	62.0 +/- 13.0	2.0 +/- 19.8
Weight (kg) (median; lower quartile to upper quartile; range)	81; 73 to 103; 45 to 152	77; 69 to 100; 38 to 130	−4;−7 to−2; −22 to + 9
Oedema			
1= none	0 (0.0%)	14(28%)	
2= mild - below knee	9 (12.5%)	24 (48%)	
3= moderate - above knee	19 (26.4%)	8 (16.0%)	
4= severe - truncal/ascites	47 (66.6%)	4 (8.0%)	
Total (n)	75	50	
Crackles			
1= clear	9 (12.5%)	24 (58.5%)	
2= crackles/wheeze base only	39 (54.2%)	16 (39.0%)	

3= crackles/wheeze whole chest	24 (33.3%)	1 (2.4%)	
Total (n)	72	41	
Patient rating breathlessness (mean; sd; range)	8.2 +/- 1.9; 0 to 10	5.2 +/- 1.8; 0 to 10	-3.0 +/-2.6; – 8 to 2
Intervention			
Dose of furosemide (mg) (mean; sd; range)	124.8 +/- 49.6 40-250	136.6 +/- 48.8 40-300	
Days of subcutaneous furosemide			
Median; lower quartile to upper quartile; range		10; 6 to 14; 1 to 49	
Site changed (median; lower quartile to upper quartile; range)		1; 0 to 2; 0 to 10	
Adverse events (n = 130)			
Total site reactions		31 (23.8%)	
Infection		4 (3.1%)	
Self-limiting mild reactions*		18 (13.8%)	
Practical problems**		6 (4.6%)	
Documented but not described***		7 (5.4%)	
Total (n)		130	

*erythema 11 (8.5%); bleeding 1 (1.5%); swelling 1 (0.8%); trauma 1 (0.8%)
** dislodged 5 (3.8%); leaking 1 (0.8%)
*** therefore counted as mild

DISCUSSION

We build on previous data[9] demonstrating effective, safe use of CSCI-furosemide, delivered within current resources (staff, equipment, medication). Clinically important weight loss, improved signs and symptoms, and support for preferred place of care was achieved. Nearly a quarter had site reactions but most were mild.

Our findings compare well with the BHF pilot study[8] which recorded a median 2.2kg (0.2 – 15.4kg) loss over a similar duration; average 7 days, range 1 to 32 days. Just under two-thirds of the IV interventions were clinically effective. The BHF pilot had more people with NYHA III (55% [BHF] vs 29% [our data]). People with NYHA IV disease and agreed ceilings of treatment (standard in our service) may have higher hospital transfer thresholds. This may explain the 20% hospital admissions in the BHF pilot. Our findings are consistent with a previous report (n =36)[12] with average 4Kg weight loss respectively (average 11 days' CSCI-furosemide).

A proprietary buffered formulation (pH of 7.4) has been developed to minimize tissue irritation. The following studies all used this buffered solution. Two studies[10] showed

almost 100% subcutaneous bioavailability: i) a proof-of-concept study and ii) a pivotal pharmacokinetic/pharmacodynamics study. None reported skin problems in the proof-of-concept study. In the pivotal study mild erythema (9/16) and skin irritation (6/16) was reported.[10] Another pilot study reported no skin irritation.[13] Two further pilot studies (conference abstracts only[14]) using longer administration reported reactions: i) 8 device problems and site discomfort in three participants over 48 hours; ii) 10 outpatients had 21 device/delivery issues and 18 adverse events (mostly mild site discomfort) over 7 days. Buffered solution studies included far fewer NYHA III/IV patients and infusion duration was much shorter, nevertheless, our data are comparable.

Strengths and limitations

This study represents "real-life" practice by several clinicians, over time (years) despite staff changes. Cohort B data included signs and symptoms not routinely documented in community/hospice settings.

There is no control group, and there are missing data. Our assumptions about reporting might be untrue. Calibrated weighing scales were not used, or standard procedures; self-weighing patients did so each morning, but times varied for others. Missing end-of-episode measurements may under-estimate deterioration, but clinicians anecdotally reported success. The NHS Trust is continuing the service, and other NHS Trusts have adopted/adapted our clinical guidelines.

Implications for clinical practice and research

Our benefit-safety profile is similar to the BHF IV pilot, and the early trials of the buffered solution. However, CSCI-furosemide uses clinical resources available UK-wide. A recent systematic review hails CSCI-furosemide as an important emerging intervention which, if confirmed in evaluative randomised controlled trials, would result in a "paradigm shift" in heart failure management. We present important preliminary data to inform the design of a definitive trial.

CONCLUSION

These preliminary data indicate that CSCI-furosemide for people with advanced heart failure who wish to avoid hospital admission is safe and effective. The findings should be confirmed or refuted in an adequately powered randomised controlled trial as a matter of priority.

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CONTRIBUTIONS

Concept MJJ, SP; data collection SP and other clinicians as above; data management, cleaning and analysis FB, EB, JG, MJJ; first draft FB; all authors contributed to, and agreed with the final manuscript.

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DATA AVAILABILITY Data are available on reasonable request to the corresponding author

CONFLICTS OF INTEREST The authors declare no conflicts of interest.

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