‘Subcutaneous furosemide in advanced heart failure: service improvement project’

Francesca Birch,1 Emily Boam,1,2 Sharon Parsons,3 Justin Ghosh,4 Miriam J Johnson 1

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 subcutaneous infusion of furosemide (CSCI-furosemide).

Methods Retrospective review of service improvement data. The heart failure nurse specialist, supported by the heart failure-palliative care multidisciplinary 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, 49–97; NYHA class 3 (36/116, 31%) or 4 heart failure (80/116, 69%)) received 130 episodes of CSCI-furosemide (average duration 10 days, 1–49), over half in the patient’s own home/care home (80/116, 69%) 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 (40–300 mg). The goal of treatment was achieved in (119/130, 91.5%) episodes.

The median reduction in weight was 4 kg (IQR −7 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 messages

► Subcutaneous infusion of furosemide is a promising alternative to intravenous infusion in people with advanced heart failure wishing to avoid otherwise unnecessary hospital admissions.

► Our data from a service improvement initiative show nearly all patient episodes achieved the goal of care and supported home, care home or hospice care.

► On average 4 kg in weight was lost over an average 10 days of infusion, with mainly mild skin reactions in a quarter of episodes.

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 as a hospital inpatient.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 intravenous where community services exist, or subcutaneous is a possible solution.1 A British Heart Foundation (BHF) pilot of community intravenous 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. The National Institute for Health and Care Excellence chronic heart failure guideline highlighted subcutaneous diuretic administration as a research priority area. Since then, a nearly 100% bioavailability of subcutaneous furosemide has been demonstrated and a pilot randomised controlled trial of subcutaneous versus intravenous has shown equivalent weight loss and diuresis. As there are still relatively few data to inform clinical practice, we continued our CSCI-furosemide service improvement routine data collection, 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.

Consecutive patients from a regional heart failure-palliative care multidisciplinary service (heart failure nurses, palliative physician, cardiologists) were eligible for CSCI-furosemide if they; (1) had optimised heart failure management, (2) required parenteral diuretic, (3) had a preferred place of care as home, hospice or care home and (4) 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.

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 intravenous 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; for example, if the patient was taking 120mg/24 hours oral, the CSCI prescription was 120 mg/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), 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: (1) at home/care home wishing to prevent hospital admission; (2) in hospital, aim to facilitate discharge despite continued need for parenteral diuretics, (3) in hospice, aiming to stabilise heart failure and (4) 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: (1) JVP—not visible, <3 cm, >3 cm; (2) chest crackles—clear, basal, whole chest; (3) oedema—none, mild (below knee), moderate (above knee), severe (truncal/ascites). Patient-reported breathlessness used a 0–10 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: (1) where ‘no’ was ticked, but there was descriptive text, we counted as ‘yes’ and categorised according to the description; (2) missing responses were counted as ‘no’; (3) 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 (1) adverse events as above; (2) oedema—the most severe response was counted, (3) place and goal of care discrepancies agreed (MJJ and EB) (eg, place=’home’, goal=’in hospital, aim of hospital discharge’; counted as ‘hospital’). With mutually exclusive options, data were treated as missing.

RESULTS
A total of 116 people with chronic advanced heart failure (men 86 (66.2%), mean age 79 years; (SD) 10; range 49–97, 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 supplemental table 1). 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 (IQR 6–14, range 1–49). Mean daily starting dose was 125mg and 137mg at the end (range 40–300mg). 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 cm 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 to −2 kg, range −22 to +9 kgs); 8/36 (22%) had a JVP >3 cm; 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.
DISCUSSION

We build on previous data 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.

Table 1  Measures at baseline and end of episode

| Measure                                      | Baseline | End of episode (or last recorded) | Change          |
|----------------------------------------------|----------|-----------------------------------|-----------------|
| **Goal achieved**                            |          |                                   |                 |
| Yes                                          | 119 (91.5%) | 11 (8.5%)                     |                 |
| No                                           | 11 (8.5%)  | 101 (81.5%)                     |                 |
| Total (n)                                    | 130      |                                   |                 |
| **Signs and Symptoms**                       |          |                                   |                 |
| **JVP**                                      |          |                                   |                 |
| 1=not visible                                | 12 (18.5%) | 13 (36.1%)                     |                 |
| 2=≤3 cm                                      | 10 (15.4%) | 15 (41.7%)                     |                 |
| 3=≥3 cm                                      | 43 (66.2%) | 8 (22.2%)                      |                 |
| Total (n)                                    | 65       | 36                                | −2.0±15.5       |
| **Pulse (beats per minute)**                 |         |                                   |                 |
| (mean; SD)                                   | 79.0±15.0| 77.0±4.0                         | −2.0±15.5       |
| **Systolic BP (mm Hg)**                      |         |                                   |                 |
| (mean; SD)                                   | 111.0±33.0| 112.0±30.0                     | 1.0±44.6        |
| **Diastolic BP (mm Hg)**                     |         |                                   |                 |
| (mean; SD)                                   | 64.0±15.0| 62.0±13.0                        | 2.0±19.8        |
| **Weight (kg)**                              | 81; 73–103; 45 to 152 | 77; 69–100; 38–130 | −4 to −2; −22 to +9 |
| **Oedema**                                   |          |                                   |                 |
| 1=none                                       | 0 (0.0%)  | 14 (28%)                         |                 |
| 2=mild to below knee                         | 9 (12.5%) | 24 (48%)                        |                 |
| 3=moderate to above knee                     | 19 (26.4%)| 8 (16.0%)                       |                 |
| 4=severe to 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; 0–10 | 5.2±1.8; 0–10 | −3.0±2.6; −8 to 2 |
| **Intervention**                             |          |                                   |                 |
| **Dose of furosemide (mg)**                  |          |                                   |                 |
| (mean; SD; range)                            | 124.8±49.6| 136.6±48.8                     |                 |
| **Days of subcutaneous furosemide**          |          |                                   |                 |
| Median; lower quartile to upper quartile; range | 40–250    | 40–300                           |                 |
| **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.
BP, blood pressure; JVP, jugular venous pressure.

Our findings compare well with the BHF pilot study, which recorded a median 2.2 kg (0.2–15.4 kg) loss over a similar duration; average 7 days, range 1–32 days. Just under two-thirds of the intravenous 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...
Another pilot study reported no skin irritation.13 Two in the proof-of-concept study. In the pivotal study, mild pharmacodynamics study. None reported skin problems showed almost 100% subcutaneous bioavailability: (1) a important preliminary data to inform the design of a ‘paradigm shift’ in heart failure management. We present evaluative randomised controlled trials, would result in a important emerging intervention which, if confirmed in A recent systematic review hails CSCI-furosemide as an

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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ORCID iD Miriam J Johnson http://orcid.org/0000-0001-6204-9158

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Imperfections 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 underestimate deterioration, but clinicians anecdotally reported success. The National Health Service (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.

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(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 minimise tissue irritation. The following studies all used this buffered solution. Two studies showed almost 100% subcutaneous bioavailability: (1) a proof-of-concept study and (2) 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.11 Two further pilot studies (conference abstracts only19) using longer administration reported reactions: (1) eight device problems and site discomfort in three participants over 48 hours; (2) 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.

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