Active management of severe hyponatraemia is associated with improved mortality

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Abstract

Objective: Severe hyponatraemia (plasma sodium concentration, pNa <120 mmol/L) is reported to be associated with mortality rates as high as 50%. Although there are several international guidelines for the management of severe hyponatraemia, there are few data on the impact of treatment.
Design and methods: We have longitudinally reviewed rates of specialist input, active management of hyponatraemia, treatment outcomes and mortality rates in patients with severe hyponatraemia (pNa <120 mmol/L) in 2005, 2010 and 2015, and compared the recent mortality rate with that of patients with pNa 120–125 mmol/L.
Results: Between 2005 and 2010 there was a doubling in the rate of specialist referral (32 to 68%, $P = 0.003$) and an increase in the use of active management of hyponatraemia in patients with pNa <120 mmol/L (63 to 88%, $P = 0.02$), associated with a reduction in mortality from 51 to 15% ($P < 0.001$). The improved rates of intervention were maintained between 2010 and 2015, but there was no further reduction in mortality. When data from all three reviews were pooled, specialist consultation in patients with pNa <120 mmol/L was associated with a 91% reduction in mortality risk, RR 0.09 (95% CI: 0.03–0.26), $P < 0.001$. Log-rank testing on in-hospital survival in 2015 found no significant difference between patients with pNa <120 mmol/L and pNa 120–125 mmol/L ($P = 0.56$).
Conclusion: Dedicated specialist input and active management of severe hyponatraemia are associated with a reduction in mortality, to rates comparable with moderate hyponatraemia.

European Journal of Endocrinology
(2021) **184**, 9–17

Introduction

Hyponatraemia is the commonest electrolyte disturbance in clinical practice (1) and has consistently been shown to be associated with increased mortality (2, 3, 4, 5, 6). In acute severe hyponatraemia, the osmotic movement of water into the brain results in cerebral oedema, which manifests as nausea, vomiting, headache and irritability, and can rapidly progress to seizures, coma and death in up to 50% of patients (7, 8). In this emergency scenario, rapid increase in plasma sodium concentration (pNa) by 4–6 mmol/L with hypertonic saline can reduce brain swelling, reverse neurological symptoms (9) and prevent fatal brain herniation (8). A large meta-analysis and population studies have demonstrated a linear relationship between pNa and mortality risk in hyponatraemia (2, 10). Some studies have suggested that this linear relationship is not maintained at pNa <120 mmol/L (5, 11).

Hyponatraemia occurs secondary to disparate medical conditions which can present to many different specialties (12); delay in seeking specialist input can delay emergency therapy (13). Some experts have therefore recommended specialist management of hyponatraemia, in order to improve clinical outcomes. In a small, prospective interventional study, which compared the outcome of intensive specialist input with routine care of hospitalised patients with hyponatraemia, Tzoulis *et al.* reported that prompt endocrine consultation led to faster

https://eje.bioscientifica.com
https://doi.org/10.1530/EJE-20-0577

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attainment of pNa targets, and reduced length of hospital stay (14). In addition, a 2015 meta-analysis showed, for the first time, that improvement in pNa in hyponatraemic patients is associated with a reduction in overall mortality (OR: 0.57, P = 0.002); the reduction in mortality was greatest in patients with lowest pNa at baseline (15). However, hyponatraemia remains under-investigated and uncorrected; half of all patients enrolled in the multinational observational Hyponatraemia Registry were discharged from hospital with pNa <130 mmol/L (16).

We present the clinical and biochemical outcomes of treatment of severe hyponatraemia at three timepoints over a 10-year period, in our hospital. The data were generated by prospective audit of the effects of change in hospital policy for management of severe hyponatraemia (pNa <120 mmol/L). We also examined outcomes in a group of patients with pNa 120–125 mmol/L. Our secondary aim was to compare the most recent mortality data using these two pNa cut-offs.

Methods

Study design

This is an observational single-centre study performed in Beaumont Hospital, a 600 bed acute hospital which is the national centre for neurosurgery and renal transplant in Ireland. We included consecutive patients who were admitted with, or who developed severe hyponatraemia (pNa <120 mmol/L), during three review periods over 10 years. We chose this pNa cut-off, as some studies have failed to demonstrate any further increase in mortality risk as pNa falls below this threshold (5, 11). Patients with moderate hyponatraemia (pNa 120–125 mmol/L) admitted during the same time served as a comparator group, chosen because this range of hyponatraemia has been shown to be associated with the highest risk of mortality (11).

The three review periods were as follows:

1. 2005, 6 months: This audit was conducted prior to the development of hospital policy for the endocrine service to offer consultation service and offer take over care of patients with pNa <120 mmol/L, in order to facilitate active management.
2. 2010, 6 months: A prospective review of the impact of the 2005 intervention, prior to a further change in hospital policy, to recommend that all patients with pNa <125 mmol/L should be referred to an Endocrinologist.
3. 2015, 9 months: A prospective observational study to assess the impact of an education package on the approach to investigation and management of hyponatraemia, based on 2013 guidelines for bolus hypertonic saline treatment of patients with hyponatraemia and clinical signs and symptoms of cerebral encephalopathy (9, 17).

The study was approved by Beaumont Hospital Ethics Committee.

Specific laboratory-designed computer software was used to search for hospital in-patients with severe hyponatraemia (pNa <120 mmol/L) and moderate hyponatraemia (pNa 120–125 mmol/L). Patients were clinically classified as hypovolaemic, euvolaemic or hypervolaemic based on standard guidelines (17). Clinical information was derived from case notes and computerised laboratory records, and used to calculate the Charlson Comorbidity Index (CCI) in the 2015 review (18). In-hospital death was defined as death occurring during the hospital stay. Cause of death was derived from the death certificate and review of the patient's clinical notes. Specialist referral was defined as formal endocrinology or nephrology consultation. Information on the treatment of hyponatraemia was collected within 48 h of admission or onset of hyponatraemia from case notes and prescription charts. Active treatment of hyponatraemia was aetiology-dependent and included; intravenous 0.9 or 3% saline, fluid restriction, tolvaptan, demeclocycline, diuresis or discontinuation of medications that had caused hyponatraemia.

Laboratory methods

PNa was measured using ion selective electrode (Olympus AU2700), normal reference range 133–146 mmol/L. Plasma and urine osmolality were measured using depression of freezing point method (2400 osmometer; Fiske, Norwood, MA).

Statistical analysis

Clinical and biochemical outcomes were compared across three timepoints, 2005, 2010 and 2015. Categorical variables are presented as number (%) and continuous variables as median (interquartile range) (as they were non-parametric). The Fishers Exact test and Chi Square test were used to compare categorical variables between groups when there were ≤5 and >5 cases in one or more groups, respectively, the Mann–Whitney to compare

continuous variables between two groups, and the Kruskal–Wallis test to compare continuous variables between three groups. The log rank test was used to compare curves for overall survival across groups which are represented as Kaplan–Meier curves. The predictors of survival were analysed by multivariate Cox proportional hazards regression. The 2015 data were analysed for differences in clinical outcomes between patients with severe and moderate hyponatraemia. Data from all three review periods were not pooled for this analysis, due to the potential impact of differences in rates of active intervention in each timepoint. A P value of <0.05 was considered as statistically significant in all tests. Statistical analysis was performed using Prism GraphPad 8.0 and cox regression analysis was performed using SPSS Version 25.0.

Results

Patient demographics are outlined in Tables 1 and 2.

Specialist referral and management of severe hyponatraemia, pNa <120 mmol/L

2005 vs 2010

There was a significant rise in the rate of specialist referral between 2005 and 2010 (32 to 68%, $P = 0.003$). This was reflected in an increase in the ascertainment of some of the key diagnostic parameters for the diagnosis of SIAD; for instance, the rate of measurement of urinary sodium concentration (UNa) increased from 29 to 79% ($P = 0.002$). The improvements in specialist referral from 2005 to 2010 led to an increase in active management of severe hyponatraemia (63 to 88%, $P = 0.02$). Ten percent (4/41) of patients with severe hyponatraemia were treated with hypertonic saline in 2005, compared with 25% (10/41) in 2010, although the difference was not statistically significant ($P = 0.14$). Length of stay in patients with severe hyponatraemia fell from 17 to 11 days between 2005 and 2010 ($P = 0.04$). There was a significant increase in pNa on discharge from hospital during the same interval, 129 to 134 mmol/L ($P = 0.01$).

Table 1 Demographics and outcomes in patients with pNa <120 mmol/L. Ascertainment of Urine osmolality (UOsm), Urinary sodium concentration (UNa) and serum cortisol was recorded in patients with euvolaemic hyponatraemia. Data are presented as median (IQR) for continuous and number (percentage) for categorical variables. A P-value of <0.05 was considered as statistically significant.

	2005	2010	2015	*P* values	
				2005 vs 2010	2010 vs 2015
n	41	41	79		
Age (years)	55 (43–70)	63 (46–78)	72 (59–81)	0.16	0.05
Nadir pNa (mmol/L)	116 (114–118)	116 (114–118)	117 (114–119)	0.8	0.4
Chronic HN	N/A	N/A	39 (49%)		
Volume category					
Euvolaemic	21 (51%)	19 (46%)	43 (54%)		
Hypovolaemic	9 (22%)	11 (27%)	22 (28%)		
Hypervolaemic	9 (22%)	11 (27%)	14 (18%)		
Undocumented	2 (5%)				
Ascertainment of:					
UOsm	10 (48%)	14 (74%)	43 (100%)	0.12	0.002
UNa	6 (29%)	15 (79%)	43 (100%)	0.002	0.007
Serum cortisol*	6 (29%)	11 (58%)	33 (97%)	0.11	<0.001
Specialist consultation	13 (32%)	25 (68%)	37 (47%)	0.003	0.05
Active treatment	26 (63%)	36 (88%)	61 (77%)	0.02	0.22
3% saline	4 (10%)	10 (24%)	7 (9%)	0.14	0.03
Tolvaptan	0	0	4 (5%)		
Length of stay (days)**	17 (11–24)	11 (6–16)	12 (7–22)	0.04	0.38
pNa on discharge** (mmol/L)	129 (117–136)	134 (131–136)	132 (130–137)	0.01	0.54
Mortality	21 (51%)	6 (15%)	11 (14%)	<0.001	>0.99

*Patients on glucocorticoid therapy excluded. **Patients who died excluded.
N/A, not available; HN, hyponatraemia.

Table 2 Demographics and outcomes in patients with pNa 120–125 mmol/L. Ascertainment of Urine osmolality (UOsm), Urinary sodium concentration (UNa) and serum cortisol was recorded in patients with euvolaemic hyponatraemia. Data are presented as median (IQR) for continuous and number (percentage) for categorical variables. A *P*-value of <0.05 was considered as statistically significant.

	2005	2010	2015	*P* values	
				2005 vs 2010	2010 vs 2015
n	84	80	287		
Age (years)	61 (45–70)	66 (56–73)	71 (61–80)	0.006	0.008
Nadir pNa (mmol/L)	123 (122–124)	123 (121–124)	123 (121–125)	0.01	0.007
Chronic HN	N/A	N/A	168 (58.5%)		
Volume Category					
Euvolaemic	43 (51%)	33 (41%)	154 (54%)		
Hypovolaemic	15 (18%)	18 (23%)	77 (27%)		
Hypervolaemic	12 (14%)	20 (25%)	55 (19%)		
Undocumented	14 (17%)	9 (11%)	1		
Ascertainment of:					
UOsm	17 (40%)	16 (48%)	143 (93%)	0.03	<0.001
UNa	15 (35%)	15 (45%)	143 (93%)	0.002	<0.001
Serum cortisol*	14 (33%)	13 (39%)	112 (91%)	0.09	<0.001
Specialist consultation	22 (26%)	20 (25%)	92 (32%)	>0.99	0.27
Active treatment	29 (35%)	38 (48%)	202 (70%)	0.11	<0.001
Length of stay (days)**	9 (6–13)	8 (4–21)	10 (5–19)	0.83	0.35
pNa on discharge ** (mmol/L)	130 (128–134)	133 (130–136)	133 (130–136)	0.004	0.84
Mortality	24 (29%)	26 (33%)	27 (9%)	0.61	<0.001

*Patients on glucocorticoid therapy excluded. **Patients who died excluded.
N/A, not available. HN, hyponatraemia.

2010 vs 2015

There was no further significant change in referral or active management of severe hyponatraemia between 2010 and 2015, 68 to 47% (P = 0.05) and 88 to 77% (P = 0.22), respectively. Median length of stay and pNa on discharge were also similar in 2010 and 2015 (Table 1).

Mortality in patients with severe hyponatraemia, pNa <120 mmol/L

2005 vs 2010

The increase in specialist referral and active management of severe hyponatraemia from 2005 to 2010 was associated with a reduction in overall mortality from 51 to 15% (P < 0.001). The Kaplan–Meier curve for 30-day in-hospital survival is displayed in Fig. 1A; the log rank test showed that the 30-day in-hospital mortality in patients with severe hyponatraemia was significantly lower in 2010 compared with 2005 (P = 0.03).

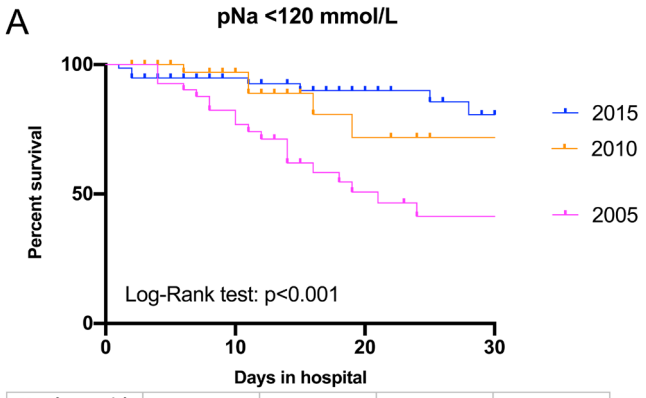
2010 vs 2015

The lower mortality rates in patients with pNa <120 mmol/L were sustained (15% in 2010 to 14% in 2015, P > 0.99). There was no difference between 30-day in-hospital survival between 2010 and 2015 on the log rank test (P = 0.75) (Fig. 1A).

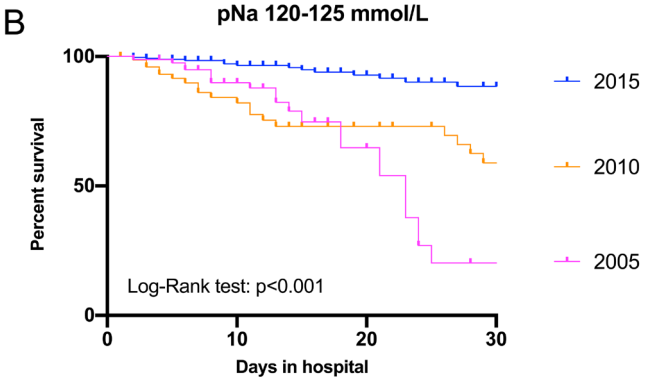
Outcomes in patients with severe hyponatraemia, pNa <120 mmol/L, pooled results from 2005, 2010 and 2015

When the results for the three review periods were pooled, overall mortality rates were 4% in patients with severe hyponatraemia with specialist referral compared with 42% in those without specialist referral, RR=0.09 (95% CI: 0.03–0.26), P < 0.001. Pooled mortality rates were 17% in patients with severe hyponatraemia who received active treatment (21/123) compared with 45% in those who did not (17/38), RR=0.38 (95% CI: 0.23–0.65), P < 0.001. A cox proportional hazards regression model was performed to determine independent risk factors for mortality, incorporating age, nadir pNa, hypervolemic hyponatraemia, specialist referral and hyponatraemia treatment; only specialist referral was associated with a significant reduction in mortality, HR=0.12 (95% CI: 0.04–0.4), P < 0.001. There was no significant association between age, nadir pNa, hypervolemic hyponatraemia and treatment of hyponatraemia and mortality risk, P = 0.99, P = 0.31, P = 0.22 and P = 0.86, respectively.

Clinical information regarding those patients with pNa <120 mmol/L who died, is presented in Table 3.



Number at risk				
2005	41	30	12	5
2010	40	25	8	4
2015	77	43	25	15



Number at risk				
2005	84	46	13	2
2010	79	40	25	15
2015	282	149	77	48

Figure 1

(A) Kaplan–Meier curve for in-hospital mortality in patients with pNa <120 mmol/L in 2005, 2010 and 2015; (B) Kaplan–Meier curve for in-hospital mortality in patients with pNa <120 mmol/L in 2005, 2010 and 2015. A full colour version of this figure is available at https://doi.org/10.1530/EJE-20-0577.

Management and outcomes in patients with pNa 120–125 mmol/L

Specialist referral rate in patients with pNa 120–125 mmol/L did not change significantly across the three time periods. There was, however, an increase in active management of hyponatraemia in this cohort, 48 to 70%, from 2010 to 2015 ($P < 0.001$). This was accompanied by a decrease in mortality, from 34 to 9% ($P < 0.001$). The Kaplan–Meier curve for 30-day in-hospital survival is displayed in Fig. 1B; the log rank test showed no significant difference between 2005 and 2010, but 30-day survival rate was significantly higher in 2015 compared with 2010 ($P < 0.001$).

Mortality in patients with pNa <120 mmol/L compared with those with pNa 120–125 mmol/L

In-hospital mortality in 2015 was compared in patients with pNa <120 mmol/L with those with pNa 120–125 mmol/L. Median age, median CCI and distribution of volume status were similar between the two groups. The relative risk for in-hospital death in patients with pNa <120 mmol/L compared with the comparator group was 1.55 (95% CI: 0.8– 2.92; $P = 0.2$). The Kaplan–Meier curve for in-hospital survival in patients with pNa <120 mmol/L and the comparator group in 2015 are displayed in Fig. 2; the log rank test showed no significant difference between mortality rates in the two groups ($P = 0.56$).

Discussion

Hyponatraemia has been shown to be associated with increased mortality in almost every published series in the literature, throughout a wide spectrum of medical conditions (2, 3, 4, 5, 6, 19, 20). In patients with hyponatraemia, there is a linear relationship between pNa and mortality risk; this has been proven in population studies such as the NHANES database (10), audits of hospitalised patients (11), and in a 2013 meta-analysis of 81 studies (2). In response to this association between hyponatraemia and mortality, consensus recommendations by expert groups have proposed a more aggressive management strategy for severe hyponatraemia. In acute hyponatraemia with neurological symptoms, bolus infusions of 3% saline rather than slow intravenous infusion, have been recommended, in order to produce a significant early rise in pNa, to reduce cerebral oedema and prevent deaths (9, 17, 21). Bolus intravenous hypertonic saline has been shown to be more effective than slow intravenous infusion in producing an acute elevation in pNa, and in restoring cognitive function (9). There have, however, been very few published data on the impact of treatment on mortality in hyponatraemia.

In this paper, we have reported clinical outcomes for patients with severe hyponatraemia (pNa <120 mmol/L) and for those with pNa 120–125 mmol/L, using data gathered during three prospective reviews over a 10-year period. Our data demonstrate that increased specialist

Table 3 Outline of deaths among patients with severe hyponatraemia (pNa <120 mmol/L).

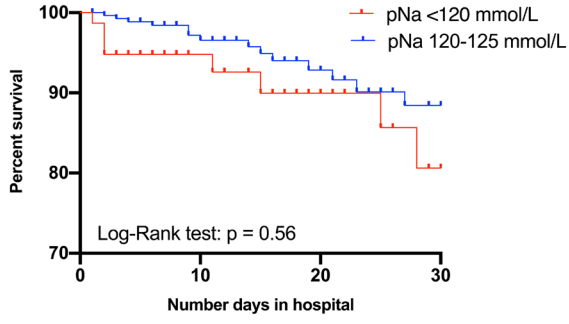
	2005	2010	2015	*P* values	
				2005 vs 2010	2010 vs 2015
n	21	6	11		
Age, years	63 (49–74)	71 (56–75)	81 (44–87)	0.52	0.19
Nadir pNa, mmol/L	114 (113–117)	116 (112–117)	117 (112–118)	0.74	0.44
Volume status, *n* (%)					
Euvolaemic	9 (43%)	1 (17%)	4 (36.5%)		
Hypovolaemic	3 (14%)	0	3 (27%)		
Hypervolaemic	7 (33%)	5 (83%)	4 (36.5%)		
Underlying causes of hyponatraemia, *n**					
Liver/heart failure	6	5	4		
Malignancy	5		1		
CNS	4		1		
Sepsis/hypovolemia	3		3		
Pulmonary fibrosis		1			
Unknown			2		
pNa <120 mmol/L at death, *n* (%)	17 (81%)	5 (83%)	5 (45%)	>0.99	0.3

*In patients with pNa <120 mmol/L who died.

input and active management of severe hyponatraemia are associated with improvements in mortality, to such a degree that mortality rates were similar to patients with hyponatraemia of moderate severity.

Our results illustrate the clinical benefits of structured specialist input to the care of patients hospitalised with hyponatraemia. Following the initial audit, the introduction of a policy of specialist referral for all patients with pNa <120 mmol/L led to a doubling in the rate of specialist consultation, and 40% increase in active management of patients with severe hyponatraemia, between 2005 and 2010. The increase in specialist input was associated with a number of positive outcomes in patients with severe hyponatraemia; a 5 mmol/L increase in median pNa on discharge, 129 vs 134 mmol/L ($P < 0.001$), a reduction in length of stay, 17 vs 11 days ($P = 0.04$), and fall in mortality rate, 51% vs 15% ($P < 0.001$). The initial improvements in these three key outcomes were maintained in 2015, despite a non-statistically significant drop in rates of specialist consultation and active management during that time. There are two potential reasons for this; first, at the time of the 2015 review, a hospital-wide observational, but not interventional, study in hyponatraemia outcomes was being conducted by the Endocrine Department. The reduction in specialist referral in 2015 may have reflected a perception that the endocrine supervision of collection of key diagnostic data, as part of the studies by Cuesta *et al.*, entailed formal consultation regarding hyponatraemia management. Secondly, with the establishment of hospital protocols for active management of hyponatraemia, physicians may have become more confident about managing hyponatraemia, without specialist intervention. Patients with severe hyponatraemia were significantly older in the 2015 analysis, 72 years vs 63 years ($P = 0.05$), reflecting an older local catchment area population, but our own (unpublished) data actually shows significantly higher rates of specialist referral and hyponatraemia-targeted treatment in older patients compared with younger controls.

We were surprised to note that the rate of active management of hyponatraemia exceeded the rate of specialist referral in 2015 by almost 2:1. We consider that the hospital-wide education has encouraged confidence in the initiation of treatment for hyponatraemia by



Number at risk				
pNa <120 mmol/L	77	43	25	15
pNa 120-125 mmol/L	282	149	77	48

Figure 2
Kaplan–Meier curve for in-hospital mortality in patients with pNa <120 mmol/L (severe) and pNa 120–125 mmol/L (moderate) in 2015. A full colour version of this figure is available at https://doi.org/10.1530/EJE-20-0577.

non-specialists. Increasingly, specialist referral was sought only when protocol-driven treatment failed or in cases of complex hyponatraemia. This may explain why endocrinology intervention was not associated with reduced duration of hospital stay, as specialist opinion was only sought in difficult or complex cases, in whom standard treatment had not reached targets. In contrast, a previous prospective interventional study showed that prompt specialist input in patients with hyponatraemia significantly reduces time to correction of hyponatraemia and shortens length of hospital stay, by a median of four days (14). Our data supports the findings of Tzoulis *et al.*, but we have additionally demonstrated a significant reduction in mortality in patients with severe hyponatraemia associated with specialist input. Indeed, when cox regression analysis was applied to pooled data from all three review periods, only specialist referral was independently associated with improvements in in-hospital survival.

In the most recent review period, the mortality in patients with pNa <120 mmol/L was reduced to levels which are similar to those in patients with moderate hyponatraemia (pNa 120–125 mmol/L) (Fig. 2). This contrasts with historical data, which showed higher death rates, of up to 50%, in patients with severe hyponatraemia (22) and mortality rates of 80% in patients with neurological symptoms who are not actively managed (23). In addition, large meta-analysis and population studies have demonstrated a linear relationship between plasma sodium and risk of death (10, 15). However, more recent interventional data suggests that this relationship is less robust at pNa <120 mmol/L, suggesting that the impact of active management of hyponatraemia is reducing the high mortality from severe hyponatraemia (5, 11). Sterns and colleagues reported a mortality rate of only 8% in a series of 64 patients with pNa <110 mmol/L (24), which is much lower than the historical figures quoted by Gill and colleagues. When the authors carefully analysed each fatal case, they found that the majority of deaths were caused by the underlying causative illness rather hyponatraemia *per se* (24). These figures are similar to the mortality rate in patients with pNa <120 mmol/L of 14% that we have reported; in all but two fatal cases in our series, there were comorbidities which directly contributed to death of the patients (25). Although our data and that of Sterns and colleagues could be interpreted to support the concept that patients die 'with' rather than 'from' hyponatraemia, both of our data sets were derived from an environment where there was rapidly instituted, active management of acute hyponatraemia, which was accompanied by neurological manifestations of cerebral oedema. In other words, both data sets were derived from a patient population in whom potentially fatal hyponatraemia was dealt with, and the residual mortality was due to underlying causative disease, which was unaffected by intervention for hyponatraemia. We would therefore argue that the reduced mortality in these two papers, one sequential over time and one in comparison to historical data, argue strongly for the benefits of active management of severe hyponatraemia.

This is a single-centre study, and the data reflect altered clinical practice at a local level. However, our results concur with those of a study from another Irish centre, which recently reported improvements in mortality in over 100 000 patients presenting to an emergency department with hyponatraemia over a 15-year period (26). As no information was provided regarding aetiology or subsequent management of hyponatraemia, it is unclear what contributed to the improvements in outcome in that study. However, their results suggest that improvements in mortality in patients with hyponatraemia are not just limited to our centre.

The observational design of our study is less robust than a prospective interventional study, but our data reflect changes in real-life practice. Specialist input may not have been sought on patients receiving end-of-life care and this may have contributed to higher mortality in those without consultation, but this would be the case across all three review periods. Our analysis does not account for overall improvements in the standard of hospital-delivered care in our institution over this 10-year period, for example, improvements in stroke and cancer care. This highlights the complexity in interpreting outcomes in hyponatraemia management, as they are inherently influenced by treatment of the underlying condition. We did not capture data on rates of overcorrection, an important adverse endpoint when assessing the efficacy of intervention in hyponatraemia which could potentially be lessened by earlier specialist supervision, but this will be recorded on further reviews. Finally, it is possible that better-decision making regarding choice of treatment played a role in improvements in mortality. As the spectrum of hyponatraemia encompassed the full range of hyper-, hypo- and eu-volaemic hyponatraemia, the range of treatments utilised in the management of patients was disparate. As a result, the effects of individual treatment regimens could not be analysed to identify the pharmacological influences on the change in mortality, though the increase in the use of hypertonic saline in severe hyponatraemia is likely to have had a major influence in reduced mortality in that category.

Conclusion

We have demonstrated that the rates of active intervention for both severe and moderate hyponatraemia have increased over a 10-year period. Increased specialist management of severe hyponatraemia has been associated with a sustained reduction in mortality in severe hyponatraemia, to a rate similar to that in patients with moderate hyponatraemia. This study adds to a growing body of evidence supporting active sodium-directed intervention in patients with severe hyponatraemia, to achieve clinically important outcomes.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding
A G received an unrestricted educational grant from Pfizer and the Charitable Infirmary Charitable Trust.

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Received 8 June 2020
Revised version received 29 September 2020
Accepted 5 October 2020