New-onset hyponatraemia after surgery for traumatic hip fracture

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Abstract

Background: hyponatraemia in orthopaedic patients is common but has been poorly investigated following surgery for traumatic hip fracture. The aims of this study were to define the incidence of new-onset post-operative hyponatraemia and to investigate associations between hyponatraemia and patient demographics, medication use and duration of hospital stay.

Methods: all patients admitted to the Orthopaedic Unit for hip surgery following trauma in 2012 were retrospectively reviewed. Patients who developed post-operative hyponatraemia within 10 days of surgery were compared with patients who remained normonatraemic pre- and post-operatively.

Results: a total of 254 patients were included. Overall, this study identified a significant (P = < 0.001) mean post-operative drop in serum sodium of 1.8 mmol/l (95% CI: 1.3–2.3%) compared with pre-operative levels. The incidence of moderate (<135 mmol/l) and severe (<130 mmol/l) post-operative hyponatraemia was 27% (95% CI: 21.7–32.5%) and 9% (95% CI: 5.7–12.8%), respectively. Statistical analysis revealed significant associations between the development of post-operative hyponatraemia and: (i) proton pump inhibitor use, (ii) selective serotonin re-uptake inhibitor use and (iii) increasing number of medications. Length of hospital stay was significantly increased in patients with moderate post-operative hyponatraemia compared with normonatraemic patients (30 versus 21 days; P = < 0.001). The incidence of new-onset post-operative hyponatraemia was not significantly increased by ethnicity, gender, fracture type, functional status or operative procedure.

Conclusion: hyponatraemia after surgery for hip fracture is common and results in longer hospital stay. This study provides evidence that an average post-operative drop in serum sodium concentration should be expected in this patient group. Moreover, patients taking SSRI or PPI medications may be at increased risk of post-operative hyponatraemia.

Keywords: hyponatraemia, post-operative, orthopaedic, hip, fracture, older people

Introduction

Hyponatraemia is the most common electrolyte disorder observed in hospitalised patients [1, 2]. The reported incidence of the disorder varies with moderate (130–135 mmol/l) and more severe (<130 mmol/l) hyponatraemia reported in 15–30 and 1–4% of inpatients, respectively [3–6]. Moderate hyponatraemia is associated with non-specific symptoms of weakness, nausea, vomiting and headache. Severe hyponatraemia is associated with neurological sequelae including central pontine myelinosis, coma and death [7–9].

Electrolyte disorders can be a late complication of surgery [10]. Specifically, the post-operative period represents a significant risk for the development of hyponatraemia, with up to 25% of cases occurring during this time [11, 12]. The incidence of post-operative hyponatraemia amongst orthopaedic patients, in particular hip fracture patients, is high and results from either water retention or loss of effective solute in excess of water [13]. Both of these phenomena occur as a result of the normal physiological response to surgery [14, 15]. This results in a non-osmotic stimulus to increase release of pituitary antidiuretic hormone (ADH) leading to water retention. Post-operative levels of ADH are universally elevated compared to pre-operative levels [16]; a response that may last for several days [14]. The presence of elevated serum ADH is central for the development and maintenance of hyponatraemia, which may be exacerbated by a large number of medications, the syndrome of inappropriate antidiuretic

†Both the authors contributed equally and are joint first authors.
hormone (SIADH) and excessive hypotonic fluid administration [1, 13].

To the best of our knowledge, no previous study has investigated the incidence of new-onset hyponatraemia following surgery for traumatic hip fracture. Thus, we carried out a retrospective study to assess the relationship between these parameters; associations with functional status, length of hospital stay, medications, fracture type and operative procedure were investigated.

**Methods**

**Study population**

This retrospective cohort study took place in the orthopaedic department of Sandwell and West Midlands NHS Trust. All cases of operatively managed traumatic hip fractures in 2012 were reviewed.

Cases were identified from the National Hip Fracture Database and demographic, clinical and functional status data collected from the electronic hospital records database. Serum sodium values on admission and for 10 days post-operatively were collected. Demographic, American Society of Anesthesiologists (ASA) physical status and medication data were collected from the electronic hospital records database.

**Exclusion criteria**

Exclusion criteria were used to ensure cases of post-operative hyponatraemia were not due to pre-existing disorders of sodium balance or the result of small decreases in serum sodium values of doubtful clinical significance. Thus, patients with pre-operative hyponatraemia or post-operative hyponatraemia resulting from <5 mmol/l drop were excluded.

**Outcomes**

Normal serum sodium was defined as 135–145 mmol/l. After exclusions, patients were categorised into three groups:

Group 1 (n = 186): Normonatraemia: pre- and post-operatively

Group 2 (n = 68): Moderate hyponatraemia: normonatraemia pre-operatively, post-operative hyponatraemia (<135 mmol/l) resulting from >5 mmol/l drop

Group 3 (n = 22, subset of group 2): Severe hyponatraemia: normonatraemia pre-operatively, severe post-operative hyponatraemia (<130 mmol/l).

**Statistical analysis**

A two-tailed, paired t-test was used to compare the means of pre- and post-operative serum sodium concentrations. Trendlines in Figure 1 were calculated in Microsoft Excel using a two-point windowed average. The proportions of concomitant medication use between categorical groups was compared using $\chi^2$ or Fishers’ exact test. These tests were also used in series to calculate the relationship between concurrent medication use. The association between categorical group and increasing number of medications was analysed using $\chi^2$ for trends. A Mann–Whitney U-test analysis was performed to analyse the relationship between PPI use and polypharmacy and also to compare length of hospital stay by categorical group. The association between increasing ASA grade and post-operative change in serum sodium concentration was assessed using ANOVA. Linear regression was used to determine the change in post-operative sodium by age. Confidence intervals were calculated using exact probabilities from the binomial distribution using the Adjusted Wald method.

**Results**

A total of 373 patients were admitted for traumatic hip fracture in 2012. Thirteen patients were excluded due to incomplete data (n = 6) or non-operative management (n = 7). A further 106 patients (29%) were excluded due to pre-operative hyponatraemia (22%, n = 80) or post-operative hyponatraemia resulting from changes in serum sodium values <5 mmol/l (7%, n = 26). Thus, 254 patients were included in the study and categorised as described above. Descriptive characteristics of the study population and comparative groups are presented in Table 1. Medication use by comparative group is presented in Table 2.

**Post-operative hyponatraemia**

Moderate and severe post-operative hyponatraemia occurred in 27% (95% CI: 21.7–32.5%) and 9% (95% CI: 5.7–12.8%), respectively. The mean post-operative serum sodium of 138.6 mmol/l (95% CI: 138.02–139.15) was significantly lower ($P < 0.001$) than the mean pre-operative serum sodium of 140.4 mmol/l (95% CI: 139.97–140.75) with a
### Table 1. Descriptive characteristics of the study population and subgroups

<table>
<thead>
<tr>
<th>Overall</th>
<th>Comparative group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Degree of hyponatraemia</td>
</tr>
<tr>
<td></td>
<td>Normal (Group 1)</td>
</tr>
<tr>
<td>Number</td>
<td>254</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>82</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>207 (82)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (6)</td>
</tr>
<tr>
<td>Afro-Caribbean</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75 (30)</td>
</tr>
<tr>
<td>Female</td>
<td>179 (71)</td>
</tr>
<tr>
<td>ASA a grade</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (3)</td>
</tr>
<tr>
<td>2</td>
<td>89 (35)</td>
</tr>
<tr>
<td>3</td>
<td>134 (53)</td>
</tr>
<tr>
<td>4</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Fracture type</td>
<td></td>
</tr>
<tr>
<td>Intertrochanteric</td>
<td>84 (33)</td>
</tr>
<tr>
<td>Intracapsular displaced</td>
<td>89 (35)</td>
</tr>
<tr>
<td>Intracapsular undisplaced</td>
<td>54 (21)</td>
</tr>
<tr>
<td>Subtrochanteric/other</td>
<td>27 (11)</td>
</tr>
<tr>
<td>Surgical type</td>
<td></td>
</tr>
<tr>
<td>Arthroplasty</td>
<td>125 (49)</td>
</tr>
<tr>
<td>Internal fixation</td>
<td>129 (51)</td>
</tr>
</tbody>
</table>

Figures are number (%) unless stated otherwise.

aAmerican Association of Anaesthesiologists physical status classification system.

### Table 2. Medication use by comparative group

<table>
<thead>
<tr>
<th>Degree of hyponatraemia</th>
<th>Normal hyponatraemic Group 1 (n = 186)</th>
<th>Moderate hyponatraemic Group 2 (n = 68)</th>
<th>Severe hyponatraemic Group 3 (n = 22)</th>
<th>P-value a</th>
<th>P-value b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td>42 (23)</td>
<td>25 (37)</td>
<td>10 (46)</td>
<td>0.023 c</td>
<td>0.019 c</td>
</tr>
<tr>
<td>Diuretic</td>
<td>37 (20)</td>
<td>19 (28)</td>
<td>8 (37)</td>
<td>0.171 c</td>
<td>0.076</td>
</tr>
<tr>
<td>SSRI</td>
<td>27 (15)</td>
<td>15 (22)</td>
<td>7 (32)</td>
<td>0.121 c</td>
<td>0.03</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>4 (2)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1.0 d</td>
<td>1.0</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>6 (3)</td>
<td>2 (3)</td>
<td>1 (5)</td>
<td>0.548 d</td>
<td>0.193</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>37 (20)</td>
<td>12 (18)</td>
<td>7 (32)</td>
<td>0.688 e</td>
<td>0.193</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>5 (3)</td>
<td>3 (4)</td>
<td>2 (9)</td>
<td>0.445 d</td>
<td>0.162</td>
</tr>
<tr>
<td>Sulphonylurea</td>
<td>6 (3)</td>
<td>3 (4)</td>
<td>2 (9)</td>
<td>0.704 d</td>
<td>0.202</td>
</tr>
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<td>No. of agents</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 agents</td>
<td>86 (46)</td>
<td>24 (35)</td>
<td>5 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 agent</td>
<td>51 (27)</td>
<td>28 (41)</td>
<td>5 (23)</td>
<td>0.056 e</td>
<td>0.007 e</td>
</tr>
<tr>
<td>≥2 agents</td>
<td>49 (26)</td>
<td>26 (38)</td>
<td>12 (55)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Using both PPI and ACEi/ARB</td>
<td>13 (7)</td>
<td>8 (12)</td>
<td>6 (27)</td>
<td>0.22</td>
<td>0.009</td>
</tr>
</tbody>
</table>

PPI, proton pump inhibitor; SSRI, selective serotonin re-uptake inhibitor; ACE-I/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker.

Frequency of medication use in Group 3 has been independently compared with that of Group 1 and Group 2 resulting in the respective P-values. Figures are number (%).

aP-value for statistical test between Group 1 (normonatraemic) and Group 2 (moderately hyponatraemic).

bP-value for statistical test between Group 1 (normonatraemic) and Group 3 (severely hyponatraemic).

cχ2-test.

dFisher’s exact analysis applied.

eχ2-test for trends quoting P-value from linear by linear association (calculated in SPSS).
mean decrease in serum sodium of 1.8 mmol/l (95% CI: 1.3–2.3%). Comparison of the distribution of serum sodium concentration pre- and post-operatively is illustrated in Figure 1.

Ethnicity, gender, fracture type, ASA grade and operative procedure

When compared with the normonatraemic group, there was no statistically significant difference in ethnicity (moderate hyponatraemia: \( P = 0.571 \); severe hyponatraemia: insufficient statistical power), gender (moderate hyponatraemia: \( P = 0.205 \); severe hyponatraemia: \( P = 0.387 \); fracture type (moderate hyponatraemia: \( P = 0.660 \); severe hyponatraemia: \( P = 0.258 \); ASA grade (moderate hyponatraemia: \( P = 0.987 \); severe hyponatraemia: \( P = 0.962 \)).

Time to discharge

Mean duration of hospital stay was significantly increased (two-tailed, Mann–Whitney U-test, \( P < 0.001 \)) in moderate hyponatraemia (mean: 30 days) compared with normonatraemia (mean: 21 days). A similar trend was observed in severe hyponatraemia (26 days); however, this was not statistically significant (two-tailed, Mann–Whitney U-test, \( P = 0.147 \)).

Peri-operative use of medication known to be associated with hyponatraemia

Hyponatraemic patients were more likely to be taking one or more known hyponatraemia-inducing agents peri-operatively; however, this was only statistically significant in severe hyponatraemia (moderate hyponatraemia: \( P = 0.056 \); severe hyponatraemia, \( P = 0.007 \)). Selective serotonin reuptake inhibitor use was statistically significantly associated with severe post-operative hyponatraemia (\( P = 0.03 \)).

There was a statistically significant association between moderate (\( P = 0.023 \)) and severe (\( P = 0.019 \)) post-operative hyponatraemia and PPI use. Amongst the study population, there was a statistically significant increase in number of additional agents taken by patients on a PPI (1.02 versus 0.58 additional agents; \( P =< 0.001 \), Mann–Whitney U-test). This relationship was observed in both hyponatraemic groups (moderate hyponatraemia: On PPI: 1.12 additional agents versus No PPI: 0.63 total agents, \( P = 0.048 \); severe hyponatraemia: On PPI: 1.8 additional agents versus No PPI: 0.75 total agents, \( P = 0.021 \)).

There was a statistically significant overrepresentation of patients on both a PPI and an ACEi/ARB in severe hyponatraemia versus normonatraemia (severe hyponatraemia: six patients on ACEi/ARB + PPI, \( n =22 \); normonatraemia: 13 patients on ACEi/ARB + PPI, \( n = 186 \); \( P = 0.009 \) via \( \chi^2 \)).

The use of medications known to be associated with hyponatraemia for each patient group and the statistical comparison between groups is detailed in Table 2.

ASA grade and age

There was no statistically significant difference in ASA grade (moderate hyponatraemia: \( P = 0.216 \); severe hyponatraemia: \( P = 0.814 \)) or age (Mann–Whitney U-test: moderate hyponatraemia, \( P = 0.748 \); severe hyponatraemia, \( P = 0.734 \)) between the hyponatraemic and normonatraemic groups.

Post-operative change in sodium

There was no statistically significant difference when comparing the post-operative change in serum sodium concentration between males and females (\( t \)-test, \( P = 0.067 \)), arthroplasty and internal fixation procedures (\( t \)-test, \( P = 0.390 \)) or ASA grade (ANOVA, \( P = 0.823 \)).

Discussion

Post-operative hyponatraemia

We found higher rates of post-operative hyponatraemia following surgery for traumatic hip fracture compared with other studies in orthopaedic patients [3–6, 17]. The high levels of hyponatraemia in our study were unlikely to be explained by gender, ethnicity, fracture type and type of operative management (arthroplasty versus internal fixation) or ASA grade, which were similarly distributed in normotraemic and hyponatraemic groups, suggesting that all hip fracture patients are at risk of the condition.

Length of stay and morbidity

Length of hospital stay was increased in moderate and severe hyponatraemia, reaching statistical significance in the moderate group. This observation probably reflects the increased morbidity associated with hyponatraemia amongst hospitalised patients [7–9, 18].

Studies have demonstrated that the odds ratio of hospital death is greater in hyponatraemic orthopaedic patients than hyponatraemic patients admitted for cardiovascular, respiratory or metastatic disease [19–22]. Additional studies are needed to investigate this further.

Medications

We found a positive association between increasing burden of medications and the incidence of post-operative hyponatraemia, reaching significance in severe hyponatraemia. This is consistent with other studies that have reported an association between hyponatraemia and a wide variety of medications that lead to drug-induced SIADH or circulating volume depletion. [11, 13, 23].

Proton pump inhibitor use was significantly associated with moderate and severe hyponatraemia. However, PPI use amongst hyponatraemic patients was also significantly associated with polypharmacy, with the greatest burden of medications being observed in severe hyponatraemia. It is therefore not possible from the current study to definitively
state that PPI use is causative in the development of hyponatraemia. Prospective experimental studies are required to isolate PPI use from polypharmacy in order to identify causation. In severe hyponatraemia, PPI use was significantly associated with ACEi/ARB use. It is important to note that whilst this association was found in normonatraemic patients as well, concomitant PPI and ACEi/ARB use was significantly overrepresented in severe hyponatraemia. This may represent a synergistic risk effect of concomitant PPI and ACEi/ARB use.

A limited number of cases of PPI-induced hyponatraemia have been described [24]. The exact pathophysiological mechanism is not clear but is thought to be SIADH.

Selective serotonin reuptake inhibitor use was significantly associated with severe hyponatraemia but not with moderate hyponatraemia. This may be due to the relatively low frequency of SSRI use and further investigation is required to establish whether SSRI use is an independent risk factor for post-operative hyponatraemia in this patient population.

Post-operative hyponatraemia in surgical patients

In a large retrospective study of 10,923 surgical intensive care unit (ICU) patients, the prevalence of ICU-acquired hyponatraemia (<135 mmol/l) was 14% and occurred more commonly after emergency surgical procedures [25]. ICU-acquired hyponatraemia was independently associated with increased hospital mortality rates and longer length of stay compared with normonatraemic patients; the latter finding is analogous to the current study. An acknowledged limitation of the above retrospective study, like ours, was the inability to review fluid regimes. It is likely that post-operative patients admitted to the ICU will receive excellent fluid management. Despite this, many surgical patients are still at considerable risk of post-operative hyponatraemia. The paucity of data relating to hyponatraemia amongst orthopaedic patients available in the above study and others may reflect their poor physical status, thus precluding them from admission to higher dependency care.

Post-operative hyponatraemia in orthopaedic patients

Our study found a greater incidence of moderate (27%) and severe (9%) post-operative hyponatraemia within 10 days of surgery compared with other studies in orthopaedic patients. In a study of 180 elderly patients, Incalzi et al. [3] reported an incidence of post-operative hyponatraemia (<135 mmol/l) of 6% in the 6 days following surgery [3]. The authors of the above study restricted intravenous (IV) fluid administration to 2.5 l over the first 42 h after surgery.

Tambe et al. [4] reported an incidence of post-operative hyponatraemia, defined as serum sodium <130 mmol/l, of 3% in the 3 days following surgery. Late hyponatraemia (>72 h after surgery) represented a further 1%. This study, like ours, excluded patients with pre-operative hyponatraemia.

It is worthwhile to note that the two studies above reviewed post-operative sodium imbalance in a number of different orthopaedic injuries including hip fracture, painful prosthesis and severe knee arthritis. Interestingly, Tambe et al. [4] reported that the majority of cases of post-operative hyponatraemia (78%) occurred in hip fracture patients. The current study provides evidence that this subset of orthopaedic patients is at greater risk of post-operative hyponatraemia.

Post-operative hyponatraemia in hip fracture

An increased incidence of pre-operative hyponatraemia in hip fracture patients has been demonstrated previously [6]. In a study of 249 elderly patients admitted for traumatic hip fracture, 17% had hyponatraemia on admission. After controlling for age, hip fracture patients were over four times as likely to be hyponatraemic as patients admitted for elective hip or knee surgery.

In a study of 155 hip fracture patients admitted for surgery, Beloosesky et al. [26] found significant differences between pre- and post-operative sodium values (P = 0.004) and an incidence of post-operative hyponatraemia (<135 mEq/l) of 25%.

Using a definition of <130 mmol/l, in a study of 112 patients admitted for hip fracture, McPherson and Dunsmuir [17] found an incidence of early (first serum sodium value after surgery) post-operative hyponatraemia of 3%.

It is important to note that in the above two studies [17, 26], the incidence of post-operative hyponatraemia was limited to the first 24 h immediately following surgery [26] or first serum sodium value after surgery [17]. Since the surgical stimulus for ADH release may last for several days [14, 16], the increased incidence of hyponatraemia reported in the present study is likely to reflect the longer duration of follow-up and is a more accurate estimate of the true incidence after surgery for hip fracture.

Importantly, the statistically significant differences between pre- and post-operative serum sodium values found in the present study (P = <0.001), in combination with the fact that pre-operatively hyponatraemic patients were excluded, suggest that the operative process itself may be a risk factor for new-onset hyponatraemia.

Conclusion

This study has several limitations. First, the retrospective nature of this study may be subject to more bias and confounding factors than a prospective study. Secondly, we excluded patients with existing hyponatraemia or new-onset hyponatraemia resulting from small drops in serum sodium levels, limiting the sample size. However, this is likely to have provided a more accurate assessment of new-onset hyponatraemia after surgery for hip fracture than would otherwise have been achieved. Third, a more powerful statistical analysis may have been achieved by treating hyponatraemia as an ordinal outcome instead of as severity groups compared against normonatraemic patients. However, categorisation of patients into severity groups is more relevant to clinical practice and permitted analysis of a subset of patients with more...
severe and clinically worrying hyponatraemia. Finally, we did not review post-operative fluid management; this would have removed the potentially confounding factor of inappropriate hypotonic fluid administration as a likely cause of post-operative hyponatraemia.

In conclusion, hyponatraemia after surgery for hip fracture is common and persists for a number of days post-operatively resulting in longer hospital stay. Risk factors include increasing burden of medications with a possible increased risk from PPIs and SSRIs. New-onset hyponatraemia occurs independently of gender, operative procedure, ethnicity, fracture type or ASA grade. The operative process itself may be a risk factor and all hip fracture patients should be considered at risk of developing the condition.

Key points

- New-onset hyponatraemia occurring within 10 days of surgery affects 27% of hip fracture patients.
- Surgery for hip fracture itself may be a risk factor for new-onset hyponatraemia.
- Length of hospital stay is increased by 9 days after hip fracture surgery in hyponatraemic patients.
- New-onset hyponatraemia after surgery for hip fracture is not associated with differences in demographics or fracture type.
- Risk factors include increasing burden of medications with a possible increased risk from PPIs and SSRIs.

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Conflicts of interest

None declared.

References


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