Prophylactic anticoagulation in Guillain-Barré syndrome: too much of a good thing?

BACKGROUND
Guillain-Barré syndrome (GBS) comprises a group of acute onset immune mediated polyradiculoneuropathies that are the leading cause of acute onset paralysis in the developed world. Management incorporates supportive care of the paralysed patient and immunomodulatory treatment. Active prevention and early treatment of complications, including venous thromboembolism (VTE), may help to improve outcomes.

Over 25,000 people die in the UK each year as a result of VTE complicating a hospital admission. As a result, national guidelines have been produced to support decision-making regarding the most appropriate strategy of VTE prophylaxis, taking into account the bleeding risk associated with the use of anticoagulation. Prolonged flaccid limb weakness and the use of intravenous immunoglobulin are risk factors for the development of VTE in patients with GBS. While consensus statements regarding VTE prophylaxis in those with GBS do exist, these are often based on evidence from studies involving postoperative patients and as such do not specifically address the risk-benefit profile of various VTE prophylaxis regimens in GBS.

At a recent mortality review meeting at our institution, we discussed the case of a 45-year-old patient with GBS in the intensive treatment unit (ITU) who died as a result of bleeding from his tracheostomy. Given his acute severe flaccid paralysis, he was prescribed ‘high dose’ (175 units/kg of subcutaneous tinzaparin per day equivalent) low molecular weight heparin (LMWH) for VTE prophylaxis, as per local practice. Concern was raised that this anticoagulant regimen may have contributed to the occurrence of bleeding and that other patients may be similarly at risk. We, therefore, performed an audit to assess the use of VTE prophylaxis in this patient group.

METHODS
Consecutive patients admitted with GBS (excluding those with Miller Fisher syndrome and Miller Fisher-GBS overlap) to our institution between 2008 and 2013 were identified using hospital episode coding data. The diagnosis was confirmed by case note review. In all cases included for further analysis, a diagnosis of GBS had been made by a consultant neurologist. We gathered data from the hospital case notes using a standardised pro forma. Demographic data, diagnosis, severity of weakness at nadir and the prophylactic anticoagulation type, dose and duration were recorded in addition to occurrence of any haemorrhagic or VTE events detected as part of routine clinical practice.

RESULTS
Our initial search identified 51 patients. Nine were excluded after initial review of the notes indicated that they had Miller Fisher syndrome (8 patients) or Miller Fisher-GBS overlap (1 patient). One further patient was excluded because the diagnosis was found to be chronic inflammatory demyelinating polyneuropathy. Therefore, 41 patients with GBS were identified, and included for further data collection and analysis. The median age at onset was 53 years (range 16–82). The median inpatient stay in our institution was 37 days (range 8–329) with a total of 2889 bed-days. All were non-ambulant and had received pharmaceutical VTE prophylaxis at some point during their admission. Twenty-two patients (53.7%) received only ‘low dose’ LMWH during the entire admission (ie, 4500 units of subcutaneous tinzaparin per day equivalent). Two patients (4.9%) received only ‘high dose’ LMWH (ie, 175 units/kg of subcutaneous tinzaparin per day equivalent). Sixteen patients (39%) received courses of each. A modified Medical Research Council (MRC) sum score was calculated at nadir for all patients. This consisted of the sum of the hip flexion and shoulder abduction power scores, giving a total out of 10 (with 0 being the weakest). Those who received ‘high dose’ LMWH at some point during their admission had a mean MRC sum score at nadir of 3.6, compared to 6.0 in those who did not. This difference was statistically significant (two-tailed t test, p=0.0015). One patient had a metallic heart valve and was taking warfarin prior to admission, which was continued.

No VTE events occurred in any patient. However, 15 haemorrhagic events occurred in 10 patients (24.4%) with five patients having two separate events (summarised in table 1). Eleven of the 15 haemorrhagic events (73.3%) occurred while the patient was receiving ‘high dose’ LMWH. Of the...
Table 1  Summary of haemorrhagic events observed in a cohort of 41 patients with Guillain-Barré syndrome

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Age</th>
<th>Sex</th>
<th>Comorbidities</th>
<th>Modified MRC-sumscore at nadir (hip flexion power +shoulder abduction power) (max score=10)</th>
<th>Dependency level at nadir</th>
<th>Haemorrhagic event</th>
<th>Number of days from admission to haemorrhagic event</th>
<th>Location of patient at time of event</th>
<th>Anticoagulation with LMWH at time of event (for VTE prophylaxis)?</th>
<th>LMWH Dose at time of event*</th>
<th>Outcome (from haemorrhagic event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75</td>
<td>M</td>
<td>IHD, hypertension, Menieres disease</td>
<td>3</td>
<td>Acute neurology ward</td>
<td>Bleeding per rectum</td>
<td>69</td>
<td>Rehabilitation Ward</td>
<td>Yes</td>
<td>Low</td>
<td>Recovery</td>
</tr>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>Hypertension</td>
<td>4</td>
<td>ITU+ventilation</td>
<td>Haematuria</td>
<td>16</td>
<td>HDU</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>F</td>
<td>Hypertension</td>
<td>3</td>
<td>ITU+ventilation</td>
<td>Bleeding tracheostomy</td>
<td>28</td>
<td>ITU</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>F</td>
<td>Hypertension, previous endometrial cancer</td>
<td>2</td>
<td>ITU+ventilation</td>
<td>Bleeding per rectum</td>
<td>19</td>
<td>ITU</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>5</td>
<td>28</td>
<td>F</td>
<td></td>
<td>4</td>
<td>ITU+ventilation</td>
<td>Bleeding per rectum</td>
<td>26</td>
<td>ITU</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>M</td>
<td>Hypertension</td>
<td>4</td>
<td>ITU+ventilation</td>
<td>Bleeding tracheostomy</td>
<td>17</td>
<td>ITU</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>7</td>
<td>66</td>
<td>M</td>
<td>IHD, previous stroke</td>
<td>2</td>
<td>ITU+ventilation</td>
<td>Bleeding tracheostomy</td>
<td>22</td>
<td>ITU</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>M</td>
<td>Hypertension</td>
<td>8</td>
<td>Acute neurology ward</td>
<td>Haematuria</td>
<td>12</td>
<td>Rehabilitation ward</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>9</td>
<td>45</td>
<td>M</td>
<td></td>
<td>2</td>
<td>ITU+ventilation</td>
<td>Bleeding tracheostomy</td>
<td>4</td>
<td>Neurology ward</td>
<td>Yes</td>
<td>High</td>
<td>Recovery</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>M</td>
<td>Metallic aortic valve replacement</td>
<td>1</td>
<td>ITU+ventilation</td>
<td>Bleeding tracheostomy</td>
<td>38</td>
<td>HDU</td>
<td>No (but anticoagulated with warfarin because of heart valve)</td>
<td>NA</td>
<td>Recovery</td>
</tr>
</tbody>
</table>

Note that multiple events occurred in some patients (15 events in 10 patients).

*’High’=175 units/kg of subcutaneous tinzaparin per day equivalent. ‘Low’=4500 units of subcutaneous tinzaparin per day equivalent.

HDU, high dependency unit; IHD, ischaemic heart disease; ITU, intensive treatment unit; LMWH, low molecular weight heparin; NA, not applicable; VTE, venous thromboembolism.
patients who experienced a haemorrhagic event, a greater proportion received ‘high dose’ LMWH at some point during their admission (80%) compared to those who received only ‘low dose’ LMWH (20%), a difference that was statistically significant ($\chi^2$ test, $p=0.014$). Twelve haemorrhagic events occurred in patients on the high dependency unit (HDU) or ITU. In patients who did have a haemorrhagic event, the mean modified MRC sum score at nadir was 3.3, compared to 5.4 in those who did not. The difference between these means was statistically significant (two-tailed $t$ test, $p=0.022$). Patients having a haemorrhagic event showed a trend towards a longer length of stay (LOS) compared to those who did not, but this difference was not statistically significant (median LOS 105 vs 28 days, Mann-Whitney U test $p=0.064$).

The most commonly encountered haemorrhagic event was tracheostomy-site bleeding, occurring in seven patients and on nine occasions in total. Seven of these events occurred while the patient was receiving ‘high dose’ LMWH. In one patient it was felt that this event contributed to death. Three of the tracheostomy-site haemorrhages required emergency bronchoscopy and three required emergency surgical intervention. In two patients a blood transfusion was required. Of the 41 patients, there were also 2 other deaths observed, both due to respiratory complications.

An iliopsoas haematoma occurred in the patient receiving warfarin. This presented with asymmetric recovery of lower limb function and necessitated prolonged rehabilitation. In others, three episodes of bleeding per rectum and two episodes of haematuria were noted.

**DISCUSSION**

Evidence-based guidelines regarding VTE prophylaxis specifically for patients with GBS are not available. The use of LMWH has been associated with a reduction in incidence of deep vein thrombosis (DVT) in one cohort of patients with GBS studied retrospectively.\(^1\) In this study, it is suggested that the risk of developing DVT is reduced from around 30% to 6% with the use of LMWH. However, the dosage regimen was not stated and the incidence of any complications associated with the use of LMWH was not reported.

VTE did not occur in our study population, all of whom received some form of prophylactic anticoagulation. However, haemorrhagic events were observed commonly and particularly in those who received a high dose of LMWH during their admission. Haemorrhagic events were most commonly observed in those patients with a tracheostomy or requiring care in HDU or ITU. One death occurred in a patient suffering from a bleeding tracheostomy who was receiving ‘high dose’ LMWH at the time of the event.

Our study has a number of limitations. It was conducted in a retrospective manner and inaccurate coding could mean some cases were missed. Furthermore, given the relative rarity of GBS, numbers are small and it is not possible to indicate how many VTE’s may have been prevented by the anticoagulation regimens used. It is also possible that the apparent association we observed between the use of ‘high dose’ LMWH and the occurrence of haemorrhagic events could be confounded by other factors which were not taken in to account such as the patient’s body mass index or abnormalities in clotting parameters. Additionally, it is possible that those with more severe GBS may be more prone to haemorrhagic events regardless of anticoagulant regimen used. The case mix of the study population may have been affected by the fact that our institution is a tertiary neurosciences centre and a number of patients were admitted as a transfer from other units. Data regarding events that occurred prior to admission to our unit or after discharge were not collected and as such additional complications may have been missed.

Our study raises concern about the risk of haemorrhagic events complicating LMWH use for VTE prophylaxis in patients with GBS. We feel that this should be taken into account when deciding on the most appropriate strategy for VTE prophylaxis. While there has been an appropriate increased focus on reducing the occurrence of avoidable VTE in hospitalised patients, further work is required (particularly addressing the limitations of this study) to define the optimal method of prophylaxis for patients with GBS to ensure that the intended benefits outweigh potential risks.

**REFERENCES**


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*J Neurol Neurosurg Psychiatry* 2016 87: 795-797 originally published online July 17, 2015
doi: 10.1136/jnnp-2015-310815

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