Original Article

National survey on thromboprophylaxis and anticoagulant or antiplatelet management in neurosurgical and neurocritical patients

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Abstract
Objectives: To determine the protocols used by Spanish anaesthesiologists for thromboprophylaxis and anticoagulant or antiplatelet drugs management in neurosurgical or neurocritical care patients.

Materials and methods: An online survey with 22 questions, with one or multiple options, launched by the Neuroscience Subcommittee of the Spanish Anaesthesia Society and available between June and October 2012.

Results: Of the 73 hospitals included in the National Hospitals Catalogue, a valid response to the online questionnaire was received by 41 anaesthesiologists from 37 sites (response rate 50.7%). Only one response per site was used. A specific protocol was available in 27% of these centres. Mechanical thromboprophylaxis is used, intraoperatively or postoperatively, in 80%, and pharmacological treatment is used by 75% of respondents. Enoxaparin was the most frequent heparin used in craniotomy patients (78%). Craniotomies were performed maintaining acetylsalicylic acid treatment in patients with coronary stents and double anti-platelet treatment in half of the centres.


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Introduction

Although the incidence of venous thromboembolism (VTE) in neurosurgical patients can be as high as 50%, the safety of pharmacologic thromboprophylaxis in these patients compared with orthopaedic surgery patients, for example, is unclear. The controversy is due to the morbidity accompanying the onset of haemorrhage in neurocritical patients or any neurosurgical procedure, and the risk of permanent complications or even death. The risk of VTE becoming symptomatic in patients that have undergone intracranial surgery can be as high as 31%. These patients are considered to be at high risk for developing VTE during the postoperative period. This is particularly true of patients undergoing craniotomy for tumour resection. Patients undergoing spinal surgery are also at risk from procedure-related factors, such as the "tuck" position in which the hips and knees are flexed, or from spinal cord retraction.

The VTE prevention method of choice in neurosurgery has traditionally been mechanical thromboprophylaxis, such as graduated compression stockings (GCS) and/or intermittent pneumatic compression (IPC) systems. The risk of bleeding associated with low-molecular-weight heparins (LMWH) has limited their use in neurosurgery. Nevertheless, pharmacologic thromboprophylaxis has been used in many patients is recent years, although opinions differ greatly with regard to clinical practice. No clinical evidence is currently available on the best management strategy for neurosurgical patients on chronic anticoagulant or antiplatelet therapy at high risk for thrombosis (with mechanical heart valves, comorbid atrial fibrillation, history of VTE, thrombophilia or coronary stent). Vitamin K antagonist oral anticoagulants should be replaced with LMWH as bridging therapy. In patients previously treated with antiplatelet agents or new oral anticoagulants, however, this is not the established approach. In 2011, the Spanish Society of Anaesthesiology and Intensive Care Medicine (SEDAR) published clinical
practice guidelines on the perioperative management of non-cardiac surgery patients receiving antiplatelet agents. These recommendations included a strategy for patients scheduled for high bleeding risk surgery, such as intracranial surgery, who are at high risk for thrombosis if antiplatelet therapy is interrupted.6 These guidelines recommend suspending clopidogrel between 3 and 5 days prior to surgery, replacing high dose acetylsalicylic acid (ASA) with a lower dose of 100 mg, and evaluating suspension of ASA from 2 to 5 days before surgery when strictly necessary.

The main aim of SEDAR’s neuroscience team was to gather information by means of a nation-wide survey on thromboprophylaxis and management of anticoagulant and antiplatelet agents in clinical practice in neurosurgical and neurocritical patients.

Materials and methods

Members of SEDAR’s neuroscience department drew up a questionnaire which was uploaded to the association’s website (http://www.anestesiados.com/encuesta-sedar-neurocirugia/) in “Google Docs” format. The survey was promoted on the association’s website, on the anestesiados.com website, and also on its corresponding Twitter account (@anestesiados). The questionnaire was aimed at the anaesthesiology departments of Spanish hospitals offering neurosurgery services, and was available online from June to October 2012. It comprised 22 questions, most of which were single- or multiple-choice. In single-choice questions, respondents had to indicate the option that best described normal clinical practice in their hospital. In the first question, anaesthesiologists were asked to name the hospital to which they were attached, in order to avoid receiving 2 questionnaires from the same centre, as only 1 questionnaire would be evaluated from each centre. If 2 questionnaires were returned by the same hospital, the department in question was asked to validate only one, and the other was discarded. The survey did not include an informed consent form, as consent was implicit in participation. The questionnaire was divided into 6 sections. The first 2 concerned mechanical VTE prophylaxis measures and pharmacologic measures in, firstly, patients not receiving prior anticoagulant/antiplatelet therapy; secondly, in patients previously receiving coumarin derivatives; and finally, in patients previously receiving antiplatelet agents. The last 4 sections contained questions on emergency interventions, minimally invasive surgery, spinal surgery, and traumatic brain injury (TBI). An example of the full questionnaire can be downloaded from Appendix (online).

The descriptive analysis of the data was performed on IBM® SPSS® v. 19.0 Statistics (IBM Corp., Armonk, NY, USA). Descriptive results are expressed as number and percentage of responses in each section. The chi-square test was performed, and statistical significance was set at \( p < 0.05 \).

Results

A total of 41 completed questionnaires were received, of which 4 were duplicates and therefore discarded. Valid online questionnaires were received from 73 anaesthesiol-
In patients previously receiving anticoagulant therapy with coumarin derivatives due to a high risk for thromboembolism (for example, documented thrombophilia, atrial fibrillation with a history of embolism, atrial fibrillation with a history of mechanical heart valves, mechanical heart valve in place for at least 3 months, etc.) who received preoperative LMWH prior to craniotomy, the last therapeutic dose of LMWH was administered 24 h prior to surgery in 51% of hospitals (Table 1).

In patients with less than 3 risk factors who were scheduled for craniotomy and had previously received antiplatelet agents as primary prevention (Table 2), most hospitals suspended ASA 5 days prior to surgery (78%). In patients with 3 or more risk factors, only 49% hospitals suspended antiplatelet therapy with ASA prior to surgery. When antiplatelet therapy was given as sole therapy for ischaemic heart disease treated with a coronary stent, only 37% of hospital suspended administration of ASA. In total, 46% of hospitals performed craniotomy while maintaining oral ASA therapy at a dose of 100 mg every 24 h. In patients with a stent who were receiving combination antiplatelet therapy with ASA and clopidogrel, 44% of hospitals suspended antiplatelet therapy, while 53% performed craniotomy while maintaining ASA therapy at a dose of 100 mg every 24 h (Table 3). The greater the number of risk factors, the higher the percentage of hospitals performing craniotomy with ASA. Statistically significant differences were found in the primary prophylaxis with less than 3 risk factors group vs primary prophylaxis with 3 or more risk factors groups ($p < 0.001$) (Fig. 3). If antiplatelet therapy was suspended prior to craniotomy in patients at high risk of thrombosis, resumption of treatment in the postoperative period varied greatly, although it was usually restarted at 24 h (46%).

With regard to minimally invasive cranial surgery, such as stereotaxic surgery, endoscopic third ventriculostomy, etc., 70% of hospitals used the same thromboprophylaxis as that used in craniotomy. The management of spinal surgery patients previously treated with antiplatelet agents is shown in Table 3. In the postoperative period, thromboprophylaxis in patients with no risk factors for VTE mainly consisted of LMWH (66%). This increased significantly to 91% in the case of patients with risk factors for VTE. In emergency craniotomy in patients taking coumarin derivatives, the most common reversal technique used was administration of prothrombin complex concentrate (80% of hospitals), followed by fresh frozen plasma (69%) and vitamin K (66%). In TBI patients with no previous anticoagulant treatment, mechanical VTE thromboprophylaxis was usually used (GCS 44%, and IPC 44%). In 35% of hospitals, thromboprophylaxis with LMWH was used, while in 24% no thromboprophylaxis measures were taken. In the case of TBI patients with previous anticoagulant treatment, the percentage of hospitals using LMWH for thromboprophylaxis increased to 52%. This was even higher than the increase observed in the use of mechanical prophylaxis in these patients (GCS 45% and PCI 42%), while the percentage of hospitals not using prophylaxis in these cases fell to just 6%.

**Discussion**

The aim of SEDAR’s neuroscience team was to gain insight into thromboprophylaxis and the management of anticoagulation and antiplatelet agents in clinical practice in neurosurgical and neurocritical patients by means of a

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Suspension and restart of perioperative treatment with low-molecular-weight heparin in patients undergoing craniotomy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (h)</td>
<td>Last preoperative dose</td>
</tr>
<tr>
<td>12</td>
<td>15 (41)</td>
</tr>
<tr>
<td>24</td>
<td>19 (51)</td>
</tr>
<tr>
<td>36</td>
<td>1 (3)</td>
</tr>
<tr>
<td>72</td>
<td>–</td>
</tr>
<tr>
<td>&gt;72</td>
<td>–</td>
</tr>
</tbody>
</table>

Results expressed as number of respondent hospitals (%).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Risk factors for thrombosis in patients with antiplatelet therapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>DM</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>ACS</td>
</tr>
<tr>
<td>Stable angina</td>
<td>PCI + stent</td>
</tr>
<tr>
<td>Stroke</td>
<td>Mechanical heart valve</td>
</tr>
<tr>
<td>AF</td>
<td>ACS: acute coronary syndrome; AF: atrial fibrillation; DM: diabetes mellitus; PCI: percutaneous coronary intervention.</td>
</tr>
</tbody>
</table>

Figure 3 | Craniotomy performed in patients maintaining acetylsalicylic acid treatment according to the results of the survey, according to indication for antiplatelet therapy. The results are expressed as the number (%) of hospital out of the total number of respondent hospitals. (A) Primary prophylaxis with less than 3 risk factors. (B) Primary prophylaxis with 3 or more risk factors. (C) Ischaemic heart disease, coronary stent and single antiplatelet therapy. (D) Ischaemic heart disease, coronary stent and combination antiplatelet therapy. |
Table 3 Management of antiplatelet therapy in neurosurgical patients.

<table>
<thead>
<tr>
<th></th>
<th>Suspend ASA</th>
<th>ASA 100 mg</th>
<th>Suspend clopidogrel</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 RF</td>
<td>C 29 (79); SS 25 (69)</td>
<td>3 (9); 8 (23)</td>
<td>37 (100); 37 (100)</td>
<td>4 (12); 3 (8)</td>
</tr>
<tr>
<td>≥3 RF</td>
<td>C 18 (49); SS 14 (38)</td>
<td>12 (31); 19 (50)</td>
<td>37 (100); 37 (100)</td>
<td>7 (20); 4 (12)</td>
</tr>
<tr>
<td>Coronary stent and sole antiplatelet agent</td>
<td>C 13 (37)</td>
<td>17 (46)</td>
<td>37 (100)</td>
<td>6 (17)</td>
</tr>
<tr>
<td>Coronary stent and combination antiplatelet agent</td>
<td>C 16 (44)</td>
<td>20 (53)</td>
<td>37 (100)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

ASA: acetylsalicylic acid; C: craniotomy; CC: spinal surgery; NA: no answer; RF: risk factors.

Results expressed as number of respondent hospitals (%).

*p < 0.001 with respect to the group with less than 3 risk factors.

A nation-wide survey. It is important to note that mechanical prophylaxis is preferred over pharmacologic strategies in these patients. We also detected a wide range of clinical practices in the different sections of the questionnaire. This difference in approach between hospitals could be explained by the scant use of specific written protocols; only 27% of hospitals had such protocols in place. Differences were observed in VTE prophylaxis in patients both with and without a history of thrombosis, and are evident in both the mechanical prophylaxis and pharmacologic strategies used.

Mechanical prophylaxis with GCS is the first-line recommendation of National Institute for Health and Clinical Excellence guidelines, and is the most commonly used mechanical strategy in respondent hospitals (83%). However, evidence to support the effectiveness of this treatment is weak, mainly due to the quality of existing studies, many of which are not double blind. The findings are hard to interpret due to the wide variety of compression methods available, and this is reflected in the heterogeneous nature of the study populations. A recent multicentre, randomised clinical trial in 2500 stroke patients was unable to prove the efficacy of mechanical methods for preventing VTE, although whether or not these findings cannot be extrapolated to surgical patients is debatable. In the ninth edition of their guidelines, the American College of Chest Physicians recommend IPC as first-line mechanical thromboprophylaxis, and specifically advise against the use of GCS in medical patients. In a systematic review of 22 clinical trials on IPC with a total of 2779 patients, this method was associated with a 64% reduction in the risk for VTE, while a more recent multicentre trial also demonstrated its effectiveness in medical patients. Correctly applied, i.e., for at least 18 h each day, IPC in the intra- and immediate postoperative period seems to be the norm in slightly over half of respondent hospitals (56% and 61%, respectively). This is greatly reduced after transfer of the patient to the ward. It is interesting to note that around 25% of respondent hospitals never use IPC. This could be due to the general preference for gradual compression stockings. Nevertheless, some aspects of IPC use are still unclear; for example, whether different compression systems are comparable, and how long the therapy should be applied after surgery.

Most (75%) respondent hospitals used LMWH for pharmacologic thromboprophylaxis following craniotomy. This is consistent with the recommendations of the American College of Chest Physicians in craniotomy patients at high risk for VTE, for example, those undergoing surgery for malignant disease. These, in fact, account for the majority of such cases. There is also evidence of consensus on which LMWH to use, this being enoxaparin (used in 78% of hospitals), followed by bemiparin, which is used to a far lesser extent. Far less agreement is found on the dosing schedule for pharmacologic prophylaxis, although 24 h post-surgery is the most frequent, and safest, regimen. It is striking that up to 11% of hospitals give LMWH 12 or 24 h before surgery in patients with no other previous risk factors, when this is even considered an alternative in orthopaedic surgery. In patients on coumarin derivatives who are given preoperative LMWH, there is little consensus on when to administer the final preoperative dose of LMWH. Perhaps the safest strategy, and one used by 51% of hospitals, is to administer it 24 h prior to surgery. In patients receiving previous anticoagulants due to a high risk for thromboembolism, the strategy for restarting the treatment in the postoperative period also varies greatly. Most (24%) hospitals, however, restart treatment 24 h post-surgery. Low-dose anticoagulants should be administered during the first week post-surgery due to the risk of bleeding. After this, dosage should be gradually increased. In patients with few risk factors, previously receiving antiplatelet therapy with ASA, most respondent hospitals suspended antiplatelet treatment 5 days prior to craniotomy. However, it is interesting to note that 9% perform surgery while administering 100 mg oral ASA every 24 h, bearing in mind its role as a primary prophylaxis. Differences in the management of these patients increase when more risk factors are present. Thus, with 3 or more risk factors, nearly 30% of hospitals perform craniotomy while maintaining 100 mg/d of oral ASA. This increases to 47% in patients with a coronary stent taking 1 antiplatelet drug, and to 55% in the case of dual antiplatelet therapy. This strategy, however, is still controversial, and only 38% of hospitals with neurosurgeons perform craniotomy with ASA in patients with previous combination antiplatelet treatment. There is a significant difference between hospitals performing craniotomy with ASA in the few risk factors/primary prophylaxis patient group and those that perform this procedure in groups with more risk factors, although the percentage of hospitals performing intracranial surgery with ASA in the primary prophylaxis/few risk factors group is...
clinically relevant. Although the decision to proceed must ultimately be taken in consensus on a case-by-case basis in high risk patients, weighing cardiovascular risk against risk of bleeding, the general recommendation is to suspend antiplatelet therapy prior to craniotomy.\textsuperscript{1,17,18} Studies have reported that suspension of antiplatelet therapy with ASA in coronary patients increases the risk of cardiovascular complications three-fold, above all between 7 and 14 days after suspension.\textsuperscript{19-21} The same is true of patients with cerebrovascular and peripheral artery disease.\textsuperscript{22,23}

In the case of clopidogrel, studies have reported an increase in cardiovascular complications and mortality at 3 months post-surgery following suspension of this drug in patients with acute coronary syndrome.\textsuperscript{24} However, a recent clinical trial in non-cardiac surgery (orthopaedic, abdominal and urological) patients found no difference in thrombotic and bleeding events between the group receiving ASA and placebo.\textsuperscript{25} Furthermore, a recent retrospective cohort study in 41,989 patients with coronary stents showed that unscheduled hospital admission is the single most important determining factor for serious adverse cardiac events. This is followed by clinical conditions such as recent myocardial infarction, heart failure, or a high score in the revised cardiac risk index.\textsuperscript{26} However, the type of stent implanted, or the time from stent to surgery was not associated with an increase in adverse cardiac events. More importantly for neurosurgical patient management, however, the study found no association between suspension of antiplatelet treatment and onset of serious cardiac events.

Renal replacement therapy has been used in patients at high risk for thrombosis in whom antiplatelet therapy has had to be temporarily suspended due to risk of bleeding. This basically involves the use of short-acting antiplatelet drugs instead of the usual ASA and clopidogrel. Nonsteroidal anti-inflammatory drugs or glycoprotein IIb/IIIa inhibitors\textsuperscript{27-29} have been used, albeit with little clinical evidence. Indeed, flurbiprofen has occasionally been used as bridging therapy in patients scheduled for craniotomy with single or combination antiplatelet therapy in only 1 respondent hospital, as shown in the survey results. Few studies have investigated the use of glycoprotein IIb/IIIa inhibitors as bridging therapy. Promising results, however, have been reported with ticofiban in non-cardiac surgery, although these studies did not include craniotomy.\textsuperscript{30,31}

Management of antiplatelet therapy in spinal surgery was similar to craniotomy, with 50% of hospitals performing surgery with ASA in patients with risk factors. LMWHs are given as thromboprophylaxis in these cases, in both at-risk and no-risk patients. This strategy is in line with the recommendations of the \textit{American College of Chest Physicians}.\textsuperscript{14} Another important aspect of thromboprophylaxis in neurosurgical patients is that thromboprophylaxis in minimally invasive surgery is largely similar (in 70% of hospitals) to the regimen used in patients scheduled for craniotomy. In emergency craniotomy in patients on anticoagulation therapy with coumarin derivatives, 80% of respondent hospitals reported using prothrombin complex for anaesthesia reversal in most cases, followed by fresh frozen plasma. Although, according to the literature, fresh frozen plasma transfusion is the most commonly-used method for emergency reversal of coumarin derivative-induced anticoagulation,\textsuperscript{32} the advantages of prothrombin complex in emergency craniotomy (possibly more effective, shorter administration time with less volume) would probably explain why this therapy was the first choice among respondent hospitals.

With regard to more specific circumstances, such a TBI with no previous anticoagulant therapy, mechanical VTE prophylaxis is usually used. It is important to note, however, that 24% of respondent hospitals do not administer any kind of prophylaxis, thus potentially, and unjustifiably, placing this population at high risk of VTE. LMWH prophylaxis is used far more often in patients previously treated with anticoagulant therapy (52%) than in patients with no previous anticoagulant treatment (35%). This highlights the risk of thrombosis in this patient population as a defining factor in hospital treatment.

One known limitation of this type of survey lies in the response rate. In our case, this was 50.7%, slightly lower than that of another survey evaluating the same population (anaesthesia in patients undergoing posterior fossa craniotomy),\textsuperscript{33} but higher than a survey on subarachnoid haemorrhage due to spontaneous aneurysmal rupture.\textsuperscript{34}

In conclusion, we believe that the results of the survey describe the most common approach to thromboprophylaxis and the management of anticoagulants and antiplatelet therapy in neurosurgical and neurocritical patients in Spain. An analysis of the results will form the basis for proposals for more standardised treatment regimens, thus reducing clinical variability. Anaesthesiologists must be directly involved in bringing about this change.

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Conflict of interests

The authors declare they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.redare.2015.08.003.

References


