

Tinzaparin vs. Fraxiparin Safety and Efficacy in Neurosurgery

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Running title:

Tinzaparin in Neurosurgical Practice

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Funding:

No funding was received.

Conflict of interest:

The authors declare no conflict of interest.

Authorship:

* Equally contributing first authors

Study design and data analysis: FW, JK, MF | Manuscript: FW; AH, DL, RO, JM | Data: AH, MG

Word count:

659

Number of figures and tables:

2 tables, no figures

Keywords:

Tinzaparin, African swine fever, heparin shortage, fraxiparin, neurosurgery, perioperative anticoagulation

Details:

I hereby confirm that the manuscript complies with all instructions to authors. The authorship requirements have been met and the final manuscript has been approved by all authors. This manuscript has not been published elsewhere and is not under consideration by another journal. We confirm adherence to ethical guidelines and that ethical approval was obtained from the IRB (see below). Conflict of interest statements for all authors have been included. We have followed the STROBE guidelines.

Abstract

Background

An outbreak of African swine fever (ASF) in China in 2020 has led to an unprecedented shortage of fraxiparin. Most patients, especially those kept in hospital for surgery, are currently treated with prophylactic anticoagulation (AC). In search of alternatives for fraxiparin, we found no sufficient data on alternatives for neurosurgical patients, such as tinzaparin of European origin. We compared fraxiparin and tinzaparin concerning adverse events (bleeding versus thromboembolic events) in neurosurgical patients.

Methods

Between 2012 and 2018, 517 neurosurgical patients with benign and malignant brain tumors as well as 297 patients with subarachnoid hemorrhage (SAH) were treated in the Department of Neurosurgery, University Hospital Leipzig receiving prophylactic anticoagulation within 48 hours. In 2015, prophylactic anticoagulation was switched from fraxiparin to tinzaparin throughout the university hospital. In a retrospective manner, the frequency and occurrence of adverse events (rebleeding and thromboembolic events) in connection with the substance used was analyzed. Statistical analysis was performed using Fisher's exact test and the chi-squared test.

Results

Rebleeding rates were similar in both fraxiparin and tinzaparin cohorts in patients being treated for meningioma, glioma, and SAH combined (8.8 vs 10.3%). Accordingly, the rates of overall thromboembolic events were not significantly different (5.5% vs 4.3%). The severity of rebleeding did not vary. There was no significant difference among subgroups when compared for deep vein thrombosis (DVT) or pulmonary embolism (PE).

Conclusion

In this retrospective study, tinzaparin seems to be a safe alternative to fraxiparin for AC in patients undergoing brain tumor surgery or suffering from SAH.

Introduction

All hospitalized patients are currently treated with prophylactic anticoagulation (AC) according to guidelines [1, 2, 3]. (Neuro-)surgical patients are at elevated risk of both thromboembolic events and intracranial rebleeding [4, 5, 6]. Data on low molecular weight heparin (LMWH) safety is therefore essential for safe prophylactic treatment. Due to an outbreak of African Swine Fever (ASF) in China [7], heparin doses are at risk of running short. Many hospitals use LMWH of Chinese production. Should there be an actual shortage, alternatives are required to maintain supply. Quite recently, the first case of ASF in wildlife was discovered in Germany, indicating a westward movement of the disease [8, 9].

In our facility, anticoagulation was formerly administered using fraxiparin. For various reasons, in 2015, the preferred medication was switched to tinzaparin, which is made in Europe. Tinzaparin supplies therefore need to be relatively independent of local ASF outbreaks [6].

Coincidentally, we retrospectively analyzed patient data on prophylactic anticoagulation from 2012 to 2018 [10], dividing the AC-treated cohorts almost equally between fraxiparin and tinzaparin. We considered a heterogenous collective of patients with acute, malignant and benign disease as representative. In this study, we present data directly comparing tinzaparin and fraxiparin in prophylactic doses regarding adverse events such as rebleeding as well as post-operative hemorrhage and thromboembolic events (TE).

Methods

The study was approved by the ethics committee of the Medical Faculty, University of Leipzig (No. 053/19-ek).

Patient selection

517 patients undergoing brain tumor surgery (278 meningioma, 239 malignant brain tumors) and 297 suffering from SAH treated at the Department of Neurosurgery University Hospital Leipzig between 2012 and 2015 were included in this retrospective study). Selection was carried out via ICD-10 registration in the hospital database. Inclusion criteria were age above

18 years and conclusive documentation as well as prophylactic anticoagulation within 48 hours after operation or hospital admission.

Diagnosis of adverse events

Cranial computer tomography (CT) or Magnetic Resonance Imaging (MRI) scans were performed within 6 hours after the initial event and within 24 hours after surgery or intervention. Patients showing new neurological deficits or unsatisfactory wake-up reaction after intervention underwent CT scans.

Diagnostic methods (e.g. duplex sonography of the veins, CT scan of the chest or abdomen) for systemic ischemia were only performed if symptoms occurred.

Anticoagulation protocol for SAH patients at our clinic

Decisions on the type and dosage of anticoagulation were based on current guidelines [1, 2, 3] and interdisciplinary bedside rounds. LMWH doses were adjusted for body weight. The standard dosage was 4500 IE (tinzaparin) or 2850 IE (fraxiparin). Patients routinely received heparin within 48 hours. Reasons for no or delayed prophylactic AC were foudroyant rebleeding, death, or treatment with flow-diverting devices or a stent necessitating different AC. Moreover, patients suffering from acute, life-threatening embolisms such as pulmonary embolism were therapeutically anticoagulated immediately.

Assessed data

Biographic: Gender, age, BMI, smoking, preexisting hypertension, preexisting therapeutic anticoagulation

Primary endpoints: Intracranial rebleeding, ischemia (cerebral and systemic)

Comorbidities and complications: Dialysis, steroid medication, acute disorder of lungs or heart, coagulation disorder

Statistical analysis

To describe the cohort, nominal parameters are displayed as percentages.

The population was dichotomously classified depending on the occurrence or nonoccurrence of adverse events (intracranial rebleeding, systemic ischemia, and cerebral ischemia).

Dichotomous parameters were analyzed using the chi-squared test or Fisher's exact test. Continuous data was analyzed with t-test, normality test was performed. P-values below 0.05 were considered statistically significant.

All analyses were computed using GraphPad QuickCalcs (www.graphpad.com), GRAPHPAD SOFTWARE, LLC, San Diego, USA, 2020.

Results

Table 1 Baseline data. Groups are comparable regarding demographic and medical data.

Patients' baseline data (n = 814)			
Demographic	Fraxiparin (n = 398)	Tinzaparin (n = 416)	p-value (t-test / Fisher's exact)
Gender	167 M (42.0%) 231 F (58.0%)	182 M (43.8%) 234 F (56.2%)	0.6205
Age (average in years)	59 ± 15.0	60 ± 14.6	0.3354
BMI (Average)	26 ± 4.5	26 ± 4.6	1.000
Underlying disease			
Malign brain tumor	106 (26.6%)	133 (32.0%)	0.0906
Meningioma	149 (37.4%)	129 (31.0%)	0.0550
SAH	143 (35.9%)	154 (37.0%)	0.7710
Medical history			
Preexisting anticoagulation	49 (12.3%)	55 (13.2%)	0.7530
Smoker	71 (17.8%)	80 (19.2%)	0.6523
Steroid medication	196 (49.2%)	190 (45.7%)	0.3259
Coagulation disorder	35 (8.8%)	34 (8.2%)	0.8018

814 received prophylactic heparinization within 48 hours. Patients' cohorts showed typical distribution of demographic data and preexisting medical conditions compared to typical cohorts of the specific disease. Cohorts showed no significant differences in baseline data. Patients with preexisting anticoagulation (n = 104, 12.8%) were not excluded from the cohorts. We performed subgroup analysis for patients with preexisting anticoagulation for meningioma, SAH and glioma individually. For meningioma and glioma surgery, therapeutic AC was paused for surgery. Logically, we found no effect on adverse events. In SAH however, preexisting anticoagulation prior to the initial event increased the risk of intracranial rebleeding (p = 0.009, OR 2.417, 95% CI of OR 1.278–4.570). This effect turned out to be insignificant when groups were combined. There was no difference between tinzaparin and fraxiparin groups (p = 0.7101).

Table 2 Adverse events of the entire cohort treated with prophylactic fraxiparin or tinzaparin. 814 patients received prophylactic anticoagulation.

Adverse events combined (n = 814)				
	Fraxiparin (n = 398)	Tinzaparin (n = 416)	p-value	
			Chi-squared	Fisher's exact
Rebleeding conservative (overall)	35 (8.8%)	43 (10.3%)	0.4996	0.4757
Rebleeding operative	13 (3.3%)	11 (2.6%)	0.7551	0.6818
Thromboembolic event (overall)	22 (5.5%)	18 (4.3%)	0.5287	0.517
Deep vein thrombosis	8 (2.0%)	4 (0.96%)	0.3513	0.2561
Pulmonary embolism	9 (2.3%)	9 (2.2%)	0.9417	1
Systemic thromboembolism	5 (1.3%)	5 (1.20%)	0.9568	1

814 patients were treated prophylactically with either fraxiparin (398) or tinzaparin (416).

Regarding hemorrhagic complications, we divided patients between those who did or did not undergo surgical treatment of rebleeding to gauge bleeding severity. The reasons for delayed or non-prophylactic treatment were severe rebleeding, acute pulmonary embolism, or securing aneurysm with a stent or flow-diverting devices, making therapeutic AC necessary. After combining the heterogenous groups of patients, differences between fraxiparin and tinzaparin were not significant. No differences were observed regarding the adverse events considered.

Discussion

Tinzaparin has been proven to be effective and safe in various patients [11, 12, 13]. Data on neurosurgical patients especially is scarce and does not compare specific substances, neither does it include different diseases [14, 15].

The study is limited due to its retrospective character. Although the number of examined patients is relatively high (n = 814), the study is not sufficiently powered to securely exclude differences between the substances investigated. Patient groups are heterogenous regarding underlying disease. Despite differences in underlying pathomechanism of rebleeding and

thromboembolism [16, 17], we assume the combined cohort applicable to heterogenous neurosurgical patient collectives. When dividing into different subgroups regarding underlying disease, we did not find specific differences.

As AC is obligatory under current guidelines, we have no control group who is not treated with AC. For obvious reasons, we cannot draw any conclusions regarding the general safety or efficacy of prophylactic AC.

Conclusion

We suppose the application of tinzaparin in neurosurgical patients to be as safe as fraxiparin. According to our data, tinzaparin is a suitable alternative to other anticoagulative substances and so could be used to counter supply shortages.

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