Newsletter

Düsseldorf, im Juli 2020

Liebe Mitarbeiterinnen, liebe Mitarbeiter,

im aktuellen Newsletter sind die Abstracts der im Monat Juni neu erschienenen Publikationen zu **COVID-19**, **Argatroban** und **HIT II** zusammengestellt.

Wie üblich weisen wir auf verschiedene interessante Arbeiten hin. Dem Newsletter vorangestellt sind wichtige Publikationen zu COVID-19.

Auch wenn die Arbeit von Arachchillage et al. (2020), in der eine erste Fallserie von 10 **COVID-19-Patienten**, die mit Argatroban antikoaguliert worden waren, schon vorgestellt wurde, soll hier noch einmal kurz auf die Arbeit eingegangen werden. Bei allen Patienten wurde Argatroban zur Antikoagulation eingesetzt, weil sich Heparin (UFH) als unwirksam erwiesen hatte (**Heparin-Resistenz**). Alle Patienten hatte thromboembolische Ereignisse (meist Lungenembolie) und erhielten in 8 Fällen eine vv-ECMO. Im Ergebnis erwies sich die Antikoagulation mit Argatroban als wirksam. Bei den Patienten traten weder neue thrombotische Komplikationen auf noch kam es zu Verschlüssen der extrakorporalen Kreisläufe (Hämodialyse; ECMO).

Liu et al. (2020) publizierten klinische Charakteristika von **COVID-19-Patienten**, um potentielle Risikofaktoren der Virusinfektion zu identifizieren, und fanden einen Zusammenhang zwischen einer **heparininduzierten Thrombozytopenie** und der Mortalität bei kritisch kranken COVID-19-Patienten. Die Thrombozytenzahl, Antikoagulation mit Heparin, HIT-Labortests und Mortalität wurden bei 61 Patienten ausgewertet. Eine schwere Thrombozytopenie wurde bei 41 % der Patienten ($< 50\times10^9$/l) festgestellt. Ein Abfall der Thrombozytenzahl um mehr als 50 % trat bei 76 % auf. Bei 96 % verlief die Infektion fatal. Insbesondere trug eine HIT, die auch ohne Gabe von Heparin als spontane HIT nachgewiesen wurde, zum Mortalitätsrisiko bei. Bei den meisten Patienten wurden Anti-Heparin-PF4-Antikörper nachgewiesen, auch wenn diese kein Heparin erhalten hatten. Die Autoren interpretieren die Befunde so, dass Anti-Heparin-PF4-Antikörper bei kritischen COVID-19-Patienten induziert werden, was zu einer progressiven Abnahme der Thrombozytenzahl führt. Die Exposition mit einer hohen Heparin-Dosis kann eine weitere schwere Thrombozytopenie mit tödlichem Ausgang auslösen. **Zur Behandlung von COVID-19-Patienten in kritischem Zustand empfehlen die Autoren ein anderes Antikoagulans als Heparin zu verwenden**.

Samarakoon et al. (2020) berichten den Fall eines 55-jährigen Patienten nach Reparatur eines offenen abdominalen Aortenaneurysmas, bei dem nach intraoperativer Gabe von unfraktioniertem Heparin und postoperativer Thromboseprophylaxe mit Enoxaparin Thromboembolien der Arteria tibialis anterior und der Arteria peronealis auftraten. Obwohl Enoxaparin nach dem Verdacht auf eine HIT auf Rivaroxaban umgestellt wurde, entwickelte der Patient während des Krankenhausaufenthaltes als Folge der HIT einen zerebralen Schlaganfall, was die Autoren auf eine mangelnde Wirksamkeit von Rivaroxaban zurückführten. Die Autoren weisen darauf hin, dass eine frühzeitige Verdachtsdiagnose aufgrund der potenziell schwerwiegenden Begleiterscheinungen (hier Thrombosen) die damit verbundene Morbidität verringern kann.

Avram et al. (2020) publizierten einen komplexen Fallbericht. Der Patient entwickelte postoperativ (gefäßchirurgischer Eingriff) eine HIT, die sowohl aus klinischer als auch serologischer Sicht bestätigt wurde. Der 4T-Score wurde mit 8 Punkten angegeben (maximal): ***T***hrombozytopenie (2 Punkte für 84% Abfall der Thrombozytenzahl nach einem Bolus von UFH (Tiefstwert 163 × 10^9/l); geeignetes ***T***iming (rasches Einsetzen einer Thrombozytopenie innerhalb von 1 Tag, nachdem der Patient 30 bis 34 Tage zuvor eine 4-tägige Heparintherapie erhalten hatte); *T*hrombose (2 Punkte für beidseitig tiefe Beinvenenthrombosen mit mikrovaskulären Thrombosen der rechten unteren Extremitäten. Nach Heparinbolus kam es zu einer anaphylaktischen Reaktion und Herzstillstand mit elektromechanischer Entkopplung – PEA[1]); und keine offensichtliche andere (o***T***her) Diagnose (2 Punkte). Die Laborbefunde bestätigten die auf dem 4T-Score basierende Verdachtsdiagnose: positive Testung in vier verschiedenen PF4-abhängige Immuno-Assays sowie in dem empfindlichen und spezifischen funktionellen Serotonin-Release-Assay (SRA). Nachdem der Patient auf Argatroban umgestellt worden war, stieg die Thrombozytenzahl an. Obwohl der Patient verstarb, illustriert der Fall jedoch mehrere faszinierende Merkmale einer HIT und die Wichtigkeit einer Kontrolle der Thrombozytenzahlen insbesondere, wenn Patienten 5 bis 30 Tage nach einer Heparin-Exposition venöse oder arterielle Thrombosen entwickeln. Eine nicht erkannte postoperative Thrombozytopenie als Folge einer verzögert einsetzenden Form einer akuten HIT deutet auf eine wahrscheinlich verspätete Diagnose der HIT hin und unterstreicht die Notwendigkeit, bei der Beurteilung thrombotischer Komplikationen in der postoperativen Phase die Thrombozytenzahl zu bestimmen.

Singh et al. (2020) publizierten den Fall einer 67-jährigen Patientin mit Myokardinfarkt und arteriellen und venösen Thrombosen der Extremitäten nach 10-tägiger prophylaktischer Gabe von Enoxaparin nach einem bilateralen Knieersatz. Nach Thrombolyse und Argatroban-Antikoagulationstherapie erholte sie sich ohne Folgeschäden. Auch hier weisen die Autoren darauf hin, dass eine tendenzielle Abnahme der Thrombozytenzahl (eine Abnahme der Thrombozytenzahl um 30% oder mehr) **und/oder das Auftreten jeder Art von Thrombosen** den Verdacht auf eine HIT erwecken sollte.

Ein weiterer interessanter Artikel beschreibt die Verwendung von Argatroban als Spüllösung („*purge solution*“) bei Patienten mit Impella-Unterstützung. Mir et al. (2020) recherchierten alle publizierten Fälle seit 2008 (N = 8), in denen UFH durch Argatroban ersetzt wurde. Die verwendeten initialen Dosierungen variierten sehr stark. Die Wirksamkeit von Argatroban war in allen Fällen gut, in zwei Fällen, in denen zusätzliche Boli von Argatroban gegeben worden war, traten jedoch massive Blutungen auf. Die Autoren ziehen die Schlussfolgerung, dass bei HIT-Patienten Argatroban als Spüllösung sicher verwendet werden kann. Blutungskomplikationen können jedoch bei zu

[1] Die elektromechanische Entkoppelung, kurz EMD oder PEA, beschreibt ein kardiologisches Phänomen, bei dem die bioelektrischen Funktionen am Herzen zwar vollkommen normal ablaufen, jedoch keine Auswurfleistung erbracht wird, d.h. kein Blut transportiert wird. Diese besondere Form des Kreislaufstillstandes stellt einen akuten Notfall dar, der unbehandelt rasch zum Tode des Patienten führt.

hoher Dosierung auftreten. Deshalb sollte die aPTT im Bereich des 3-Fachen des Ausgangswertes gehalten werden.

Abschließend ist noch auf eine Übersichtsarbeit aus dem Universitätsklinikum Tübingen zum Thema „Erworbene immunvermittelte Thrombozytopenie in der Intensivmedizin: Ein Update über relevante Diagnostik und Therapie“ hinzuweisen (Hidiatov et al., 2020). Bezogen auf die HIT wird der positive Prädiktivwert eines mittleren oder hohen 4T-Scores als unbefriedigend angesehen. Bei einem hohen klinischen Verdacht auf eine HIT sollte unverzüglich auf ein Nicht-Heparin-Antikoagulans umgestellt werden. Neben Argatroban und Danaparoid werden auch Fondaparinux und direkte orale Antikoagulanzien als „Off-label-Alternative“ aufgeführt. Lediglich bei den oralen Antikoagulanzien wird auch auf die pharmakokinetische Besonderheit niedriger Talspiegel hingewiesen, die einen unzureichenden kontinuierlichen Schutz bei HIT bewirken können (vgl. Samarakoon et al., 2020). Hier ist darauf hinzuweisen, dass bei kritisch kranken HIT-Patienten nur eine kontinuierliche (sprich intravenöse) gut steuerbare Antikoagulation eine verlässliche Antikoagulation sicherstellt.

Die Volltexte dieser Arbeiten finden Sie – soweit bisher beschafft – in unserer Literatur-Datenbank.

Mit freundlichen Grüßen

Harald O. Borbe Michael Glagow

COVID-19 – Argatroban

Suchbegriffe: “Argatroban”
“COVID-19“

12 June 2020

COVID-19; Argatroban

Anticoagulation with Argatroban in patients with acute antithrombin deficiency in severe COVID-19.

Arachchillage DJ, Remmington C, Rosenberg A, Xu T, Passariello M, Hall D, Laffan AM, Patel BV.

Br J Haematol. 2020 Jun 9. doi: 10.1111/bjh.16927. Epub ahead of print.

Abstract: COVID-19 is a highly prothrombotic disease, frequently requiring anticoagulation for prevention or treatment of thrombosis and to enable organ support (Bikdeli, Madhavan et al. 2020). The reported incidence of thrombosis in patients with COVID-19 varies considerably depending on anticoagulant regimen, severity of disease and additional risk factors such as central lines. The most commonly used in-hospital anticoagulants, unfractionated heparin (UFH) and low molecular weight heparin (LMWH), require antithrombin (AT) to exert their anticoagulant effect (Bussey and Francis 2004). Therefore, AT deficiency can result in failure achieve adequate anticoagulation with UFH or LMWH at usual doses.

PMID: 32516429 Free full text

26 June 2020

COVID-19; HIT

Heparin-induced thrombocytopenia is associated with a high risk of mortality in critical COVID-19 patients receiving heparin-involved treatment.

Liu X, Zhang X, Xiao Y, Gao T, Wang G, Wang Z, Zhang Z, Hu Y, Dong Q, Zhao S, Yu L, Zhang S, Li H, Li K, Chen W, Bian X, Mao Q, Cao C

medRxiv; 2020. DOI: 10.1101/2020.04.23.20076851.

Abstract: Background: Coronavirus infectious disease 2019 (COVID-19) has developed into a global pandemic. It is essential to investigate the clinical characteristics of COVID-19 and uncover potential risk factors for severe disease to reduce the overall mortality rate of COVID-19. Methods: Sixty-one critical COVID-19 patients admitted to the intensive care unit (ICU) and 93 severe non-ICU patients at Huoshenshan Hospital (Wuhan, China) were included in this study. Medical records, including demographic, platelet counts, heparin-involved treatments, heparin-induced thrombocytopenia-(HIT) related laboratory tests, and fatal outcomes of COVID-19 patients were analyzed and compared between survivors and nonsurvivors. Findings: Sixty-one critical COVID-19 patients treated in ICU included 15 survivors and 46 nonsurvivors. Forty-one percent of them (25/61) had severe thrombocytopenia, with a platelet count (PLT) less than 50×10^9/L, of whom 76% (19/25) had a platelet decrease of >50% compared to baseline; 96% of these patients (24/25) had a fatal outcome. Among the 46 nonsurvivors, 52.2% (24/46) had severe thrombocytopenia, compared to 6.7% (1/15) among survivors. Moreover, continuous renal replacement therapy (CRRT) could induce a significant decrease in PLT in 81.3% of critical CRRT patients (13/16), resulting in a fatal outcome. In addition, a high level of anti-heparin-PF4 antibodies, a marker of HIT, was observed in most ICU patients. Surprisingly, HIT occurred not only in patients with heparin exposure, such as CRRT, but also in heparin-naïve patients, suggesting that spontaneous HIT may occur in COVID-19. Interpretation: Anti-heparin-PF4 antibodies are induced in critical COVID-19 patients, resulting in a progressive platelet decrease. Exposure to a high dose of heparin may trigger further severe thrombocytopenia with a fatal outcome. An alternative anticoagulant other than heparin should be used to treat COVID-19 patients in critical condition.

Funding: This investigation was supported by grants 2016CB02400 and 2017YFC1201103 from the National Major Research and Development Program of China.

Keywords: COVID-19, platelet, thrombocytopenia, heparin-induced thrombocytopenia, continuous renal replacement therapy

Free full text

Argatroban

Suchbegriffe: “Argatroban”

“Heparin-induced Thrombocytopenia”

26 June 2020

Argatroban

Efficiency and safety evaluation of prophylaxes for venous thrombosis after gynecological surgery.

Yu R, Nansubuga F, Yang J, Ding W, Li K, Weng D, Wu P, Chen G, Ma D, Wei J.

Medicine (Baltimore). 2020 Jun 19;99(25):e20928. doi: 10.1097/MD.0000000000020928.

Abstract: Background: In this study, we investigate the incidence of venous thrombosis (VT), and evaluate the effectiveness and safety of 3 major thromboprophylaxes and the potential risk factors for VT in women undergoing surgery for a gynecological malignancy. Methods: We performed a randomized controlled trial of 307 patients undergoing laparoscopic surgery for gynecological malignancies at a single institution from January 2016 to October 2017. Patients were divided into 3 groups: one receiving a half dose of low-molecular-weight heparin sodium injection (FLUXUM, Alfa Wassermann, Italy) delivered by injection, one receiving a full dose of FLUXUM, and a third group receiving an Argatroban injection. Results: None of the patients in our study developed a pulmonary embolism, bleeding, or infectious complications. There were no statistical differences in the rate of deep venous thrombosis (DVT) (0%, 0%, and 2.38%) and the superficial venous thromboembolism (SVT) (15.66%, 8.97%, and 18.6%) among the 3 groups. None of the patients developed symptomatic VT. The effect of treatment on alanine aminotransferase and aspartate aminotransferase differed between the groups, with a minimal effect in the Argatroban group, and all 3 methods resulted in minimal impairment of renal function. Decreased hemoglobin, elevated levels of D-dimer, and prothrombin time were closely related to thrombogenesis. Conclusion: In conclusion, the incidence of postoperative thrombosis in gynecological malignancy among these Chinese people is not as low as we had originally presumed. Argatroban is not more effective than Parnaparin as a direct thrombin inhibitor, but it has less influence on liver function, which is beneficial for patients undergoing chemotherapy. Hemoglobin, D-dimer, and prothrombin time may be used to predict or detect thrombogenesis.

PMID: 32569239 Free full text

26 June 2020

Argatroban

Comparative Analysis of a French Prospective Series of 144 Patients with Heparin-Induced Thrombocytopenia (FRIGTIH) and the Literature.

Gruel Y, Vayne C, Rollin J, Weber P, Faille D, Bauters A, Macchi L, Alhenc-Gelas M, Lebreton A, De Maistre E, Voisin S, Gouilleux-Gruart V, Perrin J, Tardy-Poncet B, Elalamy I, Lavenu-Bombled C, Mouton C, Biron C, Ternisien C, Nedelec-Gac F, Duchemin J, De Raucourt E, Gouin-Thibault I, Rugeri L, Tardy B, Giraudeau B, Bejan-Angoulvant T, Pouplard C.

Thromb Haemost. 2020 Jun 22. doi: 10.1055/s-0040-1712957. Epub ahead of print.

Abstract: Background: Heparin-induced thrombocytopenia (HIT) is a rare complication of heparin treatments, and only a few large patient cohorts have been reported. In this study, biological and clinical data from 144 French patients with HIT were analyzed in comparison with the literature. Methods: The diagnosis of HIT was confirmed in all patients by an immunoassay combined with serotonin release assay. In the literature, only cohorts of at least 20 HIT patients published from 1992 were selected for a comparative analysis. Results: Two-thirds of patients were hospitalized in surgery and most were treated with unfractionated heparin (83.2% vs. 16.8% with low molecular weight heparin only). Thrombotic events in 54 patients (39.7%) were mainly venous (41/54). However, arterial thrombosis was more frequent after cardiac surgery (13.2% vs. 2.4% in other surgeries, p = 0.042) with a shorter recovery time (median = 3 vs. 5 days, p < 0.001). The mortality rate was lower in our series than in the 22 selected published studies (median = 6.3% vs. 15.9%). Three genetic polymorphisms were also studied, and homozygous subjects FcγRIIA RR were more frequent in patients with thrombosis (37.8 vs. 18.2% in those without thrombosis, p = 0.03). Conclusion: This study shows that the mortality rate due to HIT has recently decreased in France, possibly due to earlier diagnosis and improved medical care. It also confirms the strong association between polymorphism FcγRIIA H131R and thrombosis in HIT.

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26 June 2020

Argatroban

Preserving cannulas left in situ post ECLS

Vesper T, Weinberg A, Doellner C, Jarosz A, Haft J

Perfusion. 2020; 35(1suppl): 256

Abstract: Objective: Extracorporeal Life Support (ECLS) provides prolonged mechanical support for patients in cardiac and/or pulmonary failure. After recovery, cannulas are typically removed, however may be left in situ (CLI) in cases where there is a perceived high likelihood of returning to mechanical support or delay in decannulation. Our facility identified the need to update our guideline for the preservation of CLI to include recommendations for patients with Heparin Induced Thrombocytopenia (HIT). Methods: Our current institutional guideline for maintaining CLI was reviewed. It was determined that a diluted argatroban continuous infusion for CLI needed to be incorporated for potential HIT patients, in addition to the existing heparin 1 unit/mL cannula infusion. In addition, recommended infusion rates were reviewed and updated based on cannula diameter, length, and patient weight as compared to the current recommendation based on patient classification (i.e. neonate, pediatric, adult). Results: Over the past three years, 48 of 180 (26.6%) pediatric runs at Michigan Medicine had CLI; with HIT suspected or confirmed in 2 of 180 (0.01%). As such, we identified and addressed concerns with our current practice pertaining to patient safety, argatroban dosing and stability, and cannula characteristics including rate of infusion needed to maintain patency based on cannula length, internal diameter and side hole configuration. Safety concerns included the need for formal guidance to decrease the potential for errors with high risk medications, avoiding volume overload, and systemic anticoagulation when only cannula anticoagulation was required. Conclusions: Standardized infusion rates for argatroban and heparin were developed based on cannula size, length, and patient weight, and are as follows: heparin 1 unit/mL and argatroban 10 mcg/mL, equaling 1/100 the concentration used for systemic anticoagulation.

Free full text

26 June 2020

Argatroban

Durable LVAD implantation in a patient with HIT-II bridged with ECLS: Fantasy or reality? A case report

Fernandez Garda R, Hoy M, Rial Baston V, Monteagudo Vela M, Garcia Saez D, Simon A, Lees NJ, Hurtado Doce A

Perfusion. 2020; 35(1suppl): 105 - 106

Abstract: Objective: Extremely rare, just 2%receivingUFH develop immune-mediated reaction with serum antibodies against heparin-platelet factor4. No ideal anticoagulation strategy has been yet defined. Situation even more complex perioperatively, when upgrading to long-term MCS. Methods: To report a INTERMACS1 case as first presentation decompensated DCM with salvage pVAECMO, upgraded to LVAD already diagnosed with HITII. Placement of long-term MCS in a HIT treated patient, with its inherent periprocedural challenging management. Results: We present a fit and well 42-yearold female with decompensated heart failure after 6weeks of flu-like symptoms. ECG no ischaemic changes, coronary angiogram no significant lesions and echocardiography showed severe LV disfunction with dilated LV and LVEF< 10% with severe MR, mild RV disfyunction(TAPSE 10mm,FAC28%) with moderate TR. Initial diagnose was myocarditis, treated with steroids with no improvement. Sliding on ionotropes and diuretics, on day6 was upgraded to awake pVAECMO as ongoing cardiogenic shock, as Impella not suitable due to the presence of apicalLV thrombus.CT after cannulation showed acute pulmonary embolism with probable lingular infarction and arterial thrombosis(right posterior and anterior tibial artery occlusions).On day13,platelet count had dropped >80% and HIT score5, test was positive(2.9U/mL), confirmated by ELISA, therefore UFH switched to argatroban. On day14, loaded with levosimendan as failed several echo-guided ECLS weaning tests and on day25 underwent HeartwareRLVAD insertion as a bridge to candidacy as there were no signs of recovery. LVAD implantation was done off pump, supported by pVAECMO as CPB further complicates the situation due to higher levels of anticoagulation required intraoperatively where heparin cannot be used, titrating clotting by ACT. Bleeding issues perioperatively without need for reexploration. Developed RV failure and chest sepsis postLVAD insertion, resolved. On day9 post surgery, titration of warfarin started with no overlapping issues and aspirin dose guided by platelet activation test. Conclusions: High suspicion rate of HIT is advisable even with the use of life-sustaining mechanical support as multifactorial etiology of thrombocytopenia in critical care. Intra and perioperative management with argatroban is challenging but feasible. Demanding therapeutic management in patients requiring anticoagulation in long-term support devices.

Free full text

26 June 2020

Rivaroxaban

Heparin-induced thrombocytopaenia following abdominal aortic aneurysm repair complicated by treatment failure of rivaroxaban

Samarakoon LB, Chua F, Yap HY, Choke E

Proceedings of Singapore Healthcare. 2020, 29(2): 145 – 148

Abstract: Heparin-induced thrombocytopaenia (HIT) is a rare life-threatening complication following exposure to heparin. It is mediated by immune-mediated thrombocytopaenia due to antibody against heparin platelet factor 4 complex. Early identification of the condition and the prompt administration of appropriate treatment are important to prevent morbidity and mortality from HIT. We report a case of HIT associated with open abdominal aortic aneurysm repair causing anterior tibial artery and peroneal artery thrombosis following prophylactic use of unfractionated heparin for prophylaxis of venous thromboembolism. Even though enoxaparin was switched to rivaroxaban after HIT was suspected, our patient unfortunately developed a minor cerebrovascular accident during the hospital stay as a consequence of HIT.

Keywords: HIT, treatment failure, aortic aneurysm

Free full text

19 June 2020

Argatroban

MicroRNA-126 is a regulator of platelet-supported thrombin generation.

Zapilko V, Fish RJ, Garcia A, Reny JL, Dunoyer-Geindre S, Lecompte T, Neerman-Arbez M, Fontana P.

Platelets. 2020 Jun 12:1-10. doi: 10.1080/09537104.2020.1775804. Epub ahead of print.

Abstract: Circulating microRNA (miRNA) expression profiles correlate with platelet reactivity. MiR-126 is a promising candidate in this regard. We generated a transgenic zebrafish line with thrombocyte-specific overexpression of miR-126. Laser injury of the posterior cardinal vein of 5 days-old larvae was performed with or without antithrombotic pre-treatment. Platelet-like structures (PLS) derived from human megakaryocytes transfected with miR-126 were also evaluated for procoagulant activity. Finally, we studied the correlation between miR-126 level and thrombin generation markers in a cohort of stable cardiovascular patients. Control zebrafish developed small thrombocyte-rich thrombi at the site of vessel injury, without vessel occlusion. The miR-126 transgenic line developed an occluding thrombus in 75% (95% CI: 51-91%) of larvae. Pre-treatment with the direct thrombin inhibitor argatroban, but not aspirin, prevented vessel occlusion in the transgenic line (0% occlusion, 95%CI: 0-18%). Upon activation, human PLS showed an increased procoagulant profile after miR-126 transfection compared to control. Finally, the plasma levels of miR-126, but not a control platelet-derived miRNA, correlated with markers of in vivo thrombin generation in a cohort of 185 cardiovascular patients. Our results from three complementary approaches support a key role for miR-126 in platelet-supported thrombin generation and open new avenues in the tailoring of antithrombotic treatment.

Keywords: Platelet; platelet reactivity; thrombin; thrombosis; zebrafish.

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19 June 2020

HIT II

Venous limb gangrene and pulseless electrical activity (PEA) cardiac arrest during management of deep-vein thrombosis and progressive limb ischemic necrosis following vascular surgery.

Avram AT, Blostein MD, Hirsch AM, Warkentin TE.

Am J Hematol. 2020 Jun;95(6):712-717. doi: 10.1002/ajh.25768. Epub 2020 Mar 20.

PMID: 32112441 Free full text

19 June 2020

HIT II

Evolving concepts of pathogenesis of heparin-induced thrombocytopenia: Diagnostic and therapeutic implications.

Chong BH.

Int J Lab Hematol. 2020 Jun;42 Suppl 1:25-32. doi: 10.1111/ijlh.13223.

Abstract: Heparin-induced thrombocytopenia (HIT) is an immune reaction to heparin. It often causes severe thrombosis which may lead to limb gangrene and thrombosis-associated death. The concept of its pathogenesis has been evolving during the past five decades. Initially, HIT was thought to be caused by disseminated intravascular coagulation. Later it became clear that HIT was mediated by an immune mechanism whereby an IgG antibody induced platelet aggregation, release of procoagulant materials and consequently thrombus formation. The antigen comprises Platelet Factor 4 (PF4) and heparin which have a tendency to form ultralarge complexes. The HIT immune response has atypical features. IgG antibody appears early without IgM precedence and lasts transiently. One explanation is that there is prior priming by bacterial infection. Another unique characteristic is that it is processed as if it is a particulate antigen involving complement activation and B cells. Antigen-presenting cells/monocytes are also involved but the role of T cells is controversial. Recent advances have provided new insights into the underlying mechanisms of HIT-related thrombosis. Previously, platelets were believed to play a central role; their activation and consequently the induction of blood coagulation was the basis of the hypercoagulability in HIT. More recently, several studies have provided clear evidence that neutrophil and NETosis, monocytes and endothelial cells contribute significantly to the thrombosis in HIT. These new insights may result in development of better diagnostic laboratory assays and more effective treatments for HIT.

Keywords: NETosis; antibody; antigenic complex; heparin-induced thrombocytopenia; neutrophil; platelet; thrombosis.

PMID: 32543064 Free full text

19 June 2020

Fondaparinux

In vivo and in vitro cross-reactivity to fondaparinux in a stroke patient with IgG-PF4/heparin antibody-negative delayed-onset heparin-induced thrombocytopenia.

Krečak I, Tomac G, Škugor J, Gverić-Krečak V, Pulanić D.

Blood Transfus. 2020 Jun 4. doi: 10.2450/2020.0037-20. Epub ahead of print.

PMID: 32530398 Free full text

12 June 2020

HIT II

Rivaroxaban as an Alternative Agent for Heparin-Induced Thrombocytopenia.

Farasatinasab M, Zarei B, Moghtadaei M, Nasiripour S, Ansarinejad N, Zarei M.

J Clin Pharmacol. 2020 Jun 10. doi: 10.1002/jcph.1635. Epub ahead of print.

Abstract: Heparin-induced thrombocytopenia (HIT) is a high-risk adverse drug reaction because of its associated risk of life- and limb-threatening thrombosis. Rivaroxaban may be considered as an ideal nonheparin anticoagulant alternative for the management of HIT. In this preliminary retrospective study, the efficacy and safety of rivaroxaban to control the clinically suspected HIT (4Ts score 4 points or greater) were evaluated. Patients with chronic kidney disease, hepatic impairment, mechanical heart valves, and active bleeding were excluded. Forty-two eligible patients who received rivaroxaban for clinically suspected HIT were evaluated by medical records review, with 12-month follow-up after the first dose of rivaroxaban. End points included confirmed thrombosis (primary end point), mortality, and adverse treatment-related events. HIT-associated thrombosis was found in 17/42 (40.5%) patients before receiving rivaroxaban. After rivaroxaban therapy, platelet counts normalized in all patients, with only 1/42 (2.3%) patients developing new thrombosis. No hemorrhagic event was recorded in the patients. Twelve patients (28.6%) died, but the cause of death was not related to the thrombosis, hemorrhage, or adverse effects of rivaroxaban. Our findings are consistent with the available emerging data, suggesting that rivaroxaban is a safe and effective drug for the management of clinically suspected HIT. Rivaroxaban is a particularly valuable treatment option in developing countries, where there are issues of cost and availability of approved alternative agents.

Keywords: heparin induced thrombocytopenia; oral direct factor Xa inhibitors; rivaroxaban.

PMID: 32519800

12 June 2020

HIT II

Limitations of the particle immunofiltration assay (PIFA) test for diagnosis of heparin-induced thrombocytopenia (HIT).

Warkentin TE, Cook RJ, Greinacher A.

Am J Hematol. 2020 Jun 8. doi: 10.1002/ajh.25901. Epub ahead of print.

PMID: 32510647 Free full text

12 June 2020

HIT II

Abnormal clot microstructure formed in blood containing HIT-like antibodies.

Thomas BR, Hambly RJ, Weisel JW, Rauova L, Badiei N, Brown MR, Thornton CA, Williams PR, Hawkins K.

Thromb Res. 2020 May 20;193:25-30. doi: 10.1016/j.thromres.2020.05.029. Epub ahead of print.

Abstract: Introduction: Thrombosis is a severe and frequent complication of heparin-induced thrombocytopenia (HIT). However, there is currently no knowledge of the effects of HIT-like antibodies on the resulting microstructure of the formed clot, despite such information being linked to thrombotic events. We evaluate the effect of the addition of pathogenic HIT-like antibodies to blood on the resulting microstructure of the formed clot. Materials and methods: Pathogenic HIT-like antibodies (KKO) and control antibodies (RTO) were added to samples of whole blood containing Unfractionated Heparin and Platelet Factor 4. The formed clot microstructure was investigated by rheological measurements (fractal dimension; df) and scanning electron microscopy (SEM), and platelet activation was measured by flow cytometry. Results and conclusions: Our results revealed striking effects of KKO on clot microstructure. A significant difference in df was found between samples containing KKO (df = 1.80) versus RTO (df = 1.74; $p < 0.0001$). This increase in df was often associated with an increase in activated platelets. SEM images of the clots formed with KKO showed a network consisting of a highly branched and compact arrangement of thin fibrin fibres, typically found in thrombotic disease. This is the first study to identify significant changes in clot microstructure formed in blood containing HIT-like antibodies. These observed alterations in clot microstructure can be potentially exploited as a much-needed biomarker for the detection, management and monitoring of HIT-associated thrombosis.

Keywords: Blood coagulation; Clot microstructure; Fractal dimension; Rheology; Thrombosis.

PMID: 32505081 Free full text

05 June 2020

Argatroban

Myocardial Infarction with Limb Arterial and Venous Thrombosis in a Patient with Enoxaparin-Induced Thrombocytopenia.

Singh N, Singh Lubana S, Tsai HM.

Am J Case Rep. 2020 May 29;21:e922498. doi: 10.12659/AJCR.922498.

Abstract: BACKGROUND: Heparin, often used as an anticoagulant, acts by binding to antithrombin III. Indeed, heparin binds to a variety of proteins other than antithrombin III. Among them, platelet factor 4 can bind and neutralize the anticoagulant activity of heparin. Upon binding with heparin, platelet factor 4 undergoes a conformational change and expresses immunogenic neoepitopes that induce the generation of antibodies of the platelet factor 4 heparin complex. This immune reaction may lead to thrombocytopenia and venous, arterial, or microvascular thrombosis. However, the risk of such complications is quite variable, as it is affected not only by the source and dose of heparin and the clinical condition (e.g., cardiovascular surgery and orthopedic surgery) of the patient, but also the molecular size of the heparin formulation. Venous, arterial, and small-vessel thrombosis can lead to leg swelling, pulmonary embolism, stroke, skin necrosis, or gangrene requiring limb amputation or intestinal resection. Myocardial infarction due to coronary thrombosis also occurs, although it is less common and can be readily recognized. CASE REPORT: Heparin-induced thrombocytopenia (HIT) is a potentially life-threatening complication of heparin therapy. We report the case of a 67-year-old woman who developed ST-segment elevation myocardial infarction and thrombocytopenia within 10 days of prophylactic enoxaparin therapy after undergoing bilateral total knee replacement surgery. She also had peripheral arterial and venous thrombosis. With thrombolysis and argatroban anticoagulation therapy, she recovered without residual sequelae. CONCLUSIONS: Thrombocytopenia with coronary and other vascular thrombosis is a potentially serious complication of heparin therapy. A trend of decreased platelet count, decreased platelet count by 30% or more, and/or occurrence of any type of thrombosis should raise the suspicion of HIT. This case demonstrates that early recognition and prompt treatment of HIT can be life-saving.

PMID: 32469847 Free full text

05 June 2020

Argatroban

Argatroban as Purge Solution in Patients With Heparin-Induced Thrombocytopenia on an Impella Device, a Case Review.

Mir T, Changal KH, Smith A, Ambreen S.

Am J Ther. 2020 Jun 1. doi: 10.1097/MJT.0000000000001114. Epub ahead of print.

PMID: 32496436.

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Argatroban

Randomized trial of argatroban plus recombinant tissue-type plasminogen activator for acute ischemic stroke (ARAIS): Rationale and design.

Yang Y, Zhou Z, Pan Y, Chen H, Wang Y; ARAIS Protocol Steering Group.

Am Heart J. 2020 Apr 8;225:38-43. doi: 10.1016/j.ahj.2020.04.003. Epub ahead of print.

Abstract: Background: Previous studies have implied the efficacy and safety of argatroban plus recombinant tissue-type plasminogen activator (r-tPA) in patients with acute ischemic stroke. Further trials are needed to establish convincing conclusions in a large sample size. Research design and methods: Argatroban plus r-tPA for Acute Ischemic Stroke (ARAIS) trial is a multicenter, prospective, randomized, open-label, and blind-end point trial. The trial proposes to randomize 808 patients with acute ischemic stroke National Institutes of Health Stroke Scale (NIHSS score≥ 6 at the time of randomization) within 4.5 hours of symptom onset to receive argatroban (100 μg/kg bolus followed by an infusion of 1.0 μg/kg per minute for 48 hours) plus r-tPA or r-tPA alone. The primary end point is the proportion of patients with an excellent outcome of no clinically significant residual stroke deficits (modified Rankin scale 0-1) at 90 days. Secondary end points include the proportion of patients with a good outcome (modified Rankin scale 0-2) at 90 days, early neurological improvement (NIHSS score ≥2-point decrease) at 48 hours, early neurological deterioration (NIHSS score ≥4-point increase) at 48 hours, decrease in the NIHSS score from baseline to 14 days, and stroke recurrence or other vascular events at 90 days. Safety end points include symptomatic intracerebral hemorrhage, parenchymal hematoma type 2, and major systemic bleeding. Conclusion: ARAIS trial will evaluate whether argatroban plus r-tPA is superior to r-tPA alone in improving functional outcomes in acute ischemic stroke patients in a large sample population.

PMID: 32485328

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Argatroban

Thrombocytopenia and Thromboses in Myocardial Infarction Associated with Eptifibatide-Dependent Activating Antiplatelet Antibodies.

Puram RV, Erdil RM, Weber BN, Knelson EH, Van Beuningen AM, Wallwork R, Gilyard SN, Curtis BR, Ranganathan R, Leaf RK, Malhotra R.

Thromb Haemost. 2020 May 29. doi: 10.1055/s-0040-1712458. Epub ahead of print.

Abstract: Eptifibitide and other glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors are commonly used with dual antiplatelet therapy for high-risk percutaneous coronary interventions (PCI) in the treatment of acute coronary syndromes. Although initial clinical trials did not identify a significant incidence of thrombocytopenia following eptifibatide treatment,[1] this complication has become more recognized over time in clinical practice. We report the case of a 60-year-old man with an ST-elevation myocardial infarction (STEMI), who developed profound thrombocytopenia as well as multiple venous and arterial thromboses after exposure to eptifibatide during high-risk PCI. We demonstrate the presence and activity of eptifibatide-dependent anti-platelet antibodies in this patient and present clinical data that supports a causal link between eptifibatide and this patient's hematologic sequelae.

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05 June 2020

HIT II

Erworbene immunvermittelte Thrombozytopenie in der Intensivmedizin: Ein Update über relevante Aspekte der Diagnostik und Therapie

[Acquired immune thrombocytopenia: An update on aspects of diagnosis and management relevant for intensive care medicine].

Hidiatov O, Zlamal J, Aidery P, Bakchoul T.

Dtsch Med Wochenschr. 2020 Jun;145(11):747-753. German. doi: 10.1055/a-0962-6361. Epub 2020 Jun 3.

Abstract: Acquired thrombocytopenias represent a group of bleeding diseases, which can be mediated by immune or non-immune factors. Acquired immune thrombocytopenia (AITP) leads to an accelerated decrease in platelet count by platelet reactive antibodies arising from several mechanisms. In AITP, autoantibodies, alloantibodies or drug-dependent antibodies are usually targeting platelet surface glycoproteins. The consequence of this is a significant decrease in the number of circulating platelets, leading to clinic pathological disorders including immune thrombocytopenia, heparin-induced thrombocytopenia or drug-induced thrombocytopenia, respectively. The aforementioned disorders are characterized by a severe reduction in platelet count (< 20 × 109/l), which is, with the exception of HIT, associated with high bleeding risk. In this review we provide current insight into recent achievements regarding diagnosis and management of AITP.

Keywords: immune disease, diagnosis, treatment

PMID: 32492744