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肝素诱导的血小板减少症治疗的研究进展

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【摘要】肝素诱导的血小板减少症是一种罕见的血栓前的药物反应,由抗血小板因子 4 抗体,即一种肝素依赖的 IgG 特异性抗体,通过与血小板 Fc 受体结合而激活血小板,最终导致可能的肢体坏死或危及生命的血栓栓塞等并发症。目前主要的治疗选择包括阿加曲班、达那肝素和比伐芦定等胃肠外抗凝药物。然而近年来,新型口服抗凝药、静注人免疫球蛋白以及血浆置换等新兴治疗方法不断引起人们的关注。现对肝素诱导的血小板减少症治疗的研究进展做一概述。

【关键词】肝素诱导的血小板减少症;治疗;研究进展
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Heparin-induced Thrombocytopenia Treatment

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【**Abstract**】Heparin-induced thrombocytopenia (HIT) is a rare prethrombotic drug response that binds to platelet Fc receptors by an anti-platelet factor 4 antibody that is a heparin-dependent IgG-specific antibody. Activation of platelets ultimately leads to complications such as possible limb necrosis or life-threatening thromboembolism. Current major treatment options include parenteral anticoagulants such as argatroban, danapaparin and bivalirudin. However, in recent years, new oral anticoagulants, intravenous immunoglobulins and plasmapheresis have been emerging. This article aims to provide an overview of the research progress in HIT treatment.

【**Key words**】Heparin-induced thrombocytopenia; Treatment; Research progress

肝素诱导的血小板减少症(heparin-induced thrombocytopenia,HIT)是一种罕见的血栓前的药物反应,由抗血小板因子 4 抗体,即一种肝素依赖的 IgG 特异性抗体通过与血小板 Fc 受体结合而激活血小板,释放一些血小板源性的促凝微粒和凝血酶,引起血小板聚集,形成血栓,并最终导致可能的肢体坏死或危及生命的血栓栓塞等并发症[1]。尽管随着低分子肝素的应用,HIT 发生率有所下降,但一旦出现 HIT,若不采取积极有效的治疗方式,很可能导致患者死亡和病残。近些年来,一些抗凝药物如磺达肝癸钠、新型口服抗凝药(novel oral anticoagulants,NOACs),静注人免疫球蛋白以及血浆置换等新兴治疗方法不断引起人们的关注。现对肝素诱导的 HIT 治疗的研究进展做一概述。

1 抗凝治疗

通过酶联免疫吸附试验证实 HIT 患者体内存在抗血小板因子 4 抗体,即一种肝素依赖的 IgG 特异性抗体,它通过与血小板 Fc 受体结合激活血小板。因此,与血小板消耗增加、产生受抑或结构破坏导致出血等并发症的疾病不同,HIT 很少引起出血,但血栓形成的风险显著增高,是一种血栓前状态[1]。深静脉血栓(deep vein thrombosis,DVT)和肺栓塞(pulmonary embolism,PE)是 HIT 最常见的并发症,其次是外周动脉血栓形成和脑卒中,静脉窦血栓和内脏静脉血栓较少见。当然亦有报道骨科手术后发生 HIT 的患者出现了双侧肾上腺出血的情况,这见于更加罕见的停用肝素后,发生 HIT 或原有 HIT 加重的迟发型 HIT 或没有使用肝素的自发型 HIT(即自身免疫性 HIT),自发型 HIT 可能是因为骨科手术后膝关节软骨释放的肝素样糖胺聚糖[2]。HIT 患者出血风险很低,应该避免预防性输注血小板,否则可能增加血栓形成风险[3]。当高度怀疑 HIT 时(4Ts 评分≥4 分),及时终止任何含有肝素的相关治疗至关重要,包括低分子肝素、肝素涂层的导管和肝素冲洗等,同时开始治疗剂量的抗凝治疗[4]。ACCP 指南[4]推荐 HIT 患者使用非肝素抗凝剂如抗凝血酶依赖性Xa 因子抑制剂达那肝素(未在美国上市)、直接凝血酶抑制剂重组水蛭素、阿加曲班和仅在紧急心脏手术时使用的比伐芦定。但是 2012 年 4 月重组水蛭素因安全性等问题已经从市场上被召回[5]。目前临床上较常用于治疗 HIT 的抗凝药物为阿加曲班、达那肝素以及比伐芦定,但越来越多的研究集中在磺达肝癸钠和 NOACs 对 HIT 患者的有效性及安全性的探讨。

1.1 磺达肝癸钠

磺达肝癸钠是一种抗凝血酶依赖性的选择性Xa 因子抑制剂。ACCP 指南[4]中提到磺达肝癸钠在治疗 HIT 上的地位已经发生了一定的变化,从“仅适应证使用”到“可能用于中危甚至高危 HIT 风险的患者”。已有报道表明磺达肝癸钠用于高度怀疑急性 HIT 患者的抗凝治疗是有效且安全的,尽管目前它的适应证中并不包括 HIT[6]。一项回顾性研究中 133 例 HIT 患者接受了磺达肝癸钠治疗,其发生血栓形成和/或出血并发症的概率与其他直接凝血酶抑制剂无明显差异[7]。所以对于高度怀疑急性 HIT 的患者使用磺达肝癸钠与使用阿加曲班和达那肝素具有相似的有效性和安全性,如果不存在明显的血栓栓塞事件,预防性磺达肝癸钠剂量似乎是有效的[7-8]。HIT 中国专家共识[9]指出磺达肝癸钠用于既往有 HIT 病史的患者可能是安全的。但值得注意的是,Kang 等[7]报道的接受磺达肝癸钠治疗的 133 例高度怀疑 HIT 的患者中有 22 例(16.5%)发生血栓或与血栓相关的死亡,有 28 例(21.1%)出现大出血,然而在该研究中接受阿加曲班或达那肝素治疗的 HIT 患者血栓形成率(21.4%)和出血率(20.0%)同样较高。磺达肝癸钠一般不与抗血小板因子 4 抗体发生交叉反应,然而随着磺达肝癸钠治疗 HIT 的增加,出现了 3 例病例报道[10-12]磺达肝癸钠治疗 HIT 时在体内产生了交叉反应,导致进行性或持续性血小板减少,最终引起弥散性血管内凝血。

1.2 NOACs

目前,ACCP 指南[4]推荐对于 HIT 患者应使用维

生素 K 拮抗剂(如华法林)治疗至少 4 周,对于 HIT 合并血栓栓塞的患者则至少需要 3 个月。由于华法林能抑制生理性抗凝物蛋白 C 的产生,可能引起皮肤坏死或肢体坏疽,建议不要过早过渡到华法林治疗,一般需血小板水平达到 150×10^9/L 以上后才能口服华法林。NOACs 已经被批准用于预防和治疗静脉血栓栓塞以及降低非瓣膜性心房颤动的卒中风险,但 NOACs 治疗 HIT 的研究证据相对较少。然而维生素 K 拮抗剂的作用机制和药代动力学特征均支持首先或后续运用 NOACs 作为 HIT 的治疗选择[13]。体外实验数据表明达比加群、利伐沙班和阿哌沙班对 HIT 可能有效,但是尚需更多研究来支持这一说法[14]。目前,大多数研究数据来自一些病例报道和体外的研究,并且由于 HIT 的发生率很低,不太可能进行大型随机对照试验。利伐沙班是这些药物中研究最多的一种,正在进行的利伐沙班研究将进一步验证 NOACs 在这一领域的作用[15]。作者查阅了截至目前已发表的所有关于利伐沙班在 HIT 患者中应用的病例报道文献,整理成如下表格(表 1)。从表格中可看出几乎一半的 HIT 患者将 NOACs 作为起始治疗,另一半则作为胃肠外抗凝药物(如阿加曲班)的后续治疗。NOACs 对预防 HIT 患者发生血栓是有效的,而且出血等风险也是很低的。然而就目前研究对象的数量而言,尚不足以完全说明 NOACs 在治疗 HIT 方面的有效性和安全性,未来需更多的病例报道或随机对照试验来说明 NOACs 在 HIT 治疗方面的独特优势。

表 1 利伐沙班治疗 HIT

作者	人数	起始治疗	作为后续治疗	使用前血小板计数平均数(10^9/L)	HIT 合并血栓栓塞	结果	
						血栓	出血
Vavlukis 等[16]	1	0	1	52	1	0	0
Tardy-Poncet 等[17]	1	1	0	239	0	0	0
Abouchakra 等[18]	1	1	0	25	1	0	0
Linkins 等[19]	12	5	7	56	6	1	0
Warkentin 等[20]	10	8	2	64	5	0	0
Kopolovic 等[21]	1	0	1	30	0	0	0
Ng 等[22-23]	9	9	0	64	9	0	0
Sharifi 等[24]	9	0	9	90	4	0	0
Hantson 等[25]	1	0	1	30	1	0	0
Sartori 等[26]	1	1	0	150	1	0	0
Casan 等[27]	1	0	1	48	1	0	0
Samoš 等[28]	1	1	0	65	1	0	0
合计	48	22	22	70	30/50 (60.0%)	1/50 (2.0%)	0/50 (0%)

2 大剂量静脉注射免疫球蛋白的运用

最近对 400 多例 HIT 患者进行的一项研究表明,即使进行合理的抗凝治疗,HIT 的发病率和死亡率仍然很高[29]。尽管之前 HIT 的治疗一直强调非肝素抗凝药物的使用,但最近越来越多的关注集中在运用大剂量的静脉注射免疫球蛋白(intravenous immune globulin, IVIG)治疗严重或持续的 HIT[10,30]。对于血栓形成和出血高风险的患者(如怀孕或存在静脉窦血栓等并发症)或自身免疫性 HIT 的患者,大剂量 IVIG 联合抗凝治疗可能是一种选择[10]。酶联免疫吸附试验证实运用 IVIG 后患者体内肝素依赖的 IgG 特异性抗体仍为强阳性,这说明 IVIG 并不是封闭该抗体,而是通过竞争性抑制血小板 Fc 受体,达到抑制血小板激活的目的[30]。这一发现为新近出现的 HIT 和体内尚残留抗血小板因子 4 抗体,又需要运用肝素抗凝的急症手术患者的治疗提供了一种新的方法。美国食品药品监督管理局称 IVIG 可能存在导致血栓形成的风险,根据以前的文献报道很难确定其发生率,但最近一项包括 31 个随机对照试验,总共超过 4 000 例研究对象的大型临床荟萃分析结果表明 IVIG 并不增加动脉或静脉血栓形成的风险[31]。同样大剂量 IVIG 治疗 HIT 的研究绝大多数都是病例报道,而且治疗数量也是很有限的。所以作者查阅了近 5 年已发表的关于 IVIG 在 HIT 患者中应用的病例报道文献,整理成如下表格(表 2)。可以看出大剂量 IVIG 对于严重、持续或高血栓负荷的 HIT 患者血小板计数的快速恢复还是很有效的,它能够降低 HIT 患者发生或再发血栓栓塞,甚至出血的风险。绝大部分研究者选择 1 ~ 2 g/kg 的大剂量 IVIG 持续治疗 2 ~ 3 d,同时联合使用胃肠外抗凝药物(如阿加曲班)或后续辅以 NOACs 进行抗凝

治疗的方案。这样的一种联合用药方案可能对未来改善 HIT 患者的预后是有益的。

表 2　IVIG 治疗 HIT

作者/时间	年龄(岁)/性别	血小板计数最低值(10^9/L)	HIT 合并症	IVIG 治疗的剂量(g/kg)及持续时间(d)	IVIG 治疗后血小板计数(10^9/L)及恢复时间(d)
Warkentin 等[32],2014	24/女	18	双侧肺出血	15.0 g,3	77,4
Tvito 等[10],2015	69/男	14	PE	1.0,3	124,—
	68/男	20	DVT	1.0,—	150,9
Azimov 等[33],2017	85/女	3	DVT	1.0,2	137,5
	58/女	26	DVT、PE	1.0,3	241,5
				0.45,2	
Padmanabhan 等[30],2017	47/男	13	DVT、PE	1.0,2	164,3
	73/男	25	PE	1.0,2	177,3
	72/男	16	DVT	1.0,2	124,5
				0.5,3	
Ibrahim 等[34],2017	78/女	15	颈内静脉血栓	0.4,4	80,4
	35/女	31	—	0.4,2	—
Warkentin 等[35],2018	59/男	34	左下肢远端进行性缺血坏死	术前 90.0 g,—	—
				术后 90.0 g,—	

3　血浆置换

血浆置换用于治疗 HIT 最早可追溯到 20 世纪 80 年代,尽管如此,ACCP 指南[4]并未涉及使用血浆置换治疗 HIT 的问题;但是在美国血液成分学会最新指南中提到血浆置换作为Ⅱc 级推荐可用于 HIT 的治疗[36]。最近,它被证明可缓解 HIT 患者脑出血的临床症状并降低血栓形成等风险[37]。对于急性 HIT(血小板减少合并抗血小板因子 4 抗体阳性)和亚急性 HIT(近期出现的 HIT,血小板计数恢复正常但抗血小板因子 4 抗体阳性)需行心脏手术的患者,ACCP 指南[4]建议延迟手术或使用非肝素抗凝剂,如比伐芦定。但是对于需紧急行心室辅助装置或心脏移植的 HIT 患者,等待 50 ~ 80 d(体内抗血小板因子 4 抗体清除的中位时间)显然是不可行的。所以这时血浆置换可被用来迅速去除抗血小板因子 4 抗体并恢复血小板计数,从而减少术中以及术后相关并发症的发生率[38-39]。Ramu 等[40]报道了 3 例需紧急心脏手术的急性 HIT 患者在术前进行血浆置换,并且术中运用肝素抗凝的成功治疗案例。术前进行血浆置换,术中运用肝素和术后使用非肝素抗凝剂治疗是 HIT 的重症患者行紧急心脏手术的可选治疗方案[40]。值得注意的是,血浆置换可能会引起感染、低钙血症、大量血容量转移和血流动力学不稳定等并发症。所以血浆置换对于需要紧急手术的 HIT 患者可能是一个重要的辅助治疗方式,但同时也需注意它的相关并发症的预防和处理。

4　结语

由于 HIT 是一种住院患者中发生的少见疾病,其发生率很低,所以对于诸如 NOACs、IVIG 以及血浆置换等新兴治疗方法的研究,目前仅停留在一些成功治疗的案例或体外试验,对于这些新兴治疗方法尚需更多的病例资料以及未来可能的随机对照试验来不断验证其有效性和安全性。未来可能需解决的问题如 NOACs 作为起始治疗和后续治疗对于 HIT 患者的治疗效果有何不同;大剂量 IVIG 冲击联合后续抗凝治疗对 HIT 患者长期预后的影响以及多种联合治疗方式如 IVIG + NOACs + 静脉非肝素抗凝药物或血浆置换 + NOACs + 静脉非肝素抗凝药物对于 HIT 患者的疗效等。

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