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急性脑梗死溶栓治疗的临床进展*

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摘要: 脑梗死是一种常见的神经系统疾病,具有高发病率、高死亡率和高致残率的特点,给患者及家庭带来巨大的痛苦和经济负担,它已成为当代医学界重要的研究课题。脑梗死的治疗直接影响患者的预后,因此寻找最有效的治疗药物及方法是非常重要的。目前,在急性脑梗死溶栓治疗方面国内外已经开展了大量的实验研究,取得了良好的实验结果。本文就急性脑梗死溶栓治疗的时间窗、溶栓方法、溶栓药物及影响因素等方面进行了总结及展望。

关键词: 时间窗;溶栓方法;溶栓药物;预后影响因素

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Research Progress of Acute Ischemic Stroke Treated with Thrombolytic*

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ABSTRACT: Stroke is a common neurological diseases with high morbidity, high mortality and high morbidity characteristics, which brings great suffer and economic burden to the patients and families, and has become an important research topic in contemporary medical profession. Treatment directly affects the prognosis of patients with cerebral infarction, and thus it is very important to find the most effective treatments and methods. Currently, thrombolytic therapy in acute cerebral infarction have carried out a large number of experimental studies, and achieved good results. This paper reviewed the thrombolytic therapy in acute cerebral infarction including the time window, methods and drugs of thrombolysis, and the influencing factors of outcomes were also summarized and discussed.

Key words: Time window; Thrombolysis method; Thrombolytic; Factors influencing

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前言

在发展中国家,脑梗死是导致成年人致死率和致残率的主要原因。每年中国新出现的脑梗死患者约有 250 万人,幸存者约 750 万人,死亡人数约 170 万^[1]。脑梗死发病率的上升给中国医疗卫生系统带来了很大的负担^[2]。每年中国花费在治疗脑梗死疾病费用约 400 亿人民币。随着人口老龄化、城市化、其他的生活方式和变化,脑梗死相关的治疗成本继续成为中国医疗体系的负担。目前,在急性脑梗死溶栓治疗方面国内外已经开展了大量的实验研究,取得了良好的实验结果。发病 4.5 小时内静脉注射(Intravenous, IV)重组型组织型纤溶酶原激活剂(recombinant tissue plasminogen activator, rt-PA)能有效的治疗急性缺血性脑梗死(acute ischemic stroke, AIS)^[3-5]。30% 的溶栓患者在 3 个月内很小或者没有残疾,这种益处可以延长 1 年。本文就急性脑梗死溶栓治疗的时间窗、溶栓方法、溶栓药物及影响因素等方面进行综述。

1 溶栓时间窗发展及可能的机制

急性缺血性脑梗死(AIS)患者需要早期进行溶栓治疗,由

于研究较少,因此溶栓时间窗存在争论^[6]。美国的首例关于 IV rt-PA 的试验性研究表明安全性治疗时间窗为 90 分钟,剂量高达 1.08 mg/kg^[7]。在以后的研究中将治疗时间窗延长至 180 分钟,增加了出血概率,降低了治疗率,但是总体预后比未使用溶栓剂预后较好^[8]。美国国家研究院疾病及卒中研究所(NINDS)对 AIS 患者进行 rt-PA 溶栓治疗,将治疗时间窗分为 2 组,分别为 0-90 分钟与 91-180 分钟。经过数据分析表明,使用 rt-PA 3 个月后预后良好。在 ECASS III 安慰剂对照研究中发现 3-4 小时内静脉注射 rt-PA 的预后良好,随后将溶栓治疗时间窗扩大到 4.5 小时。2008 年 ECASS III 涉及 821 例患者,实验结果得出静脉注射 rt-PA 组与安慰剂相比,预后显著提高^[9]。

血管再通的基本机制就是缺血半暗带的存在,其特征是低灌注与细胞功能障碍,但神经元没有死亡,通过补救治疗,恢复血流供应,拯救缺血半暗带^[10,11]。临床研究表明,恢复血流目的是防止缺血半暗带形成梗死病灶^[12]。在临床试验中,90-100% 的 AIS 患者在发病 3 小时内出现缺血半暗带^[13];75-80% AIS 患者在发病 6 小时内出现的缺血半暗带^[3]。然而,缺血半暗带因为患者的不同而有所差异,因为它依赖于多种因素,如血

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管损害的位置^[14],缺血性病变的位置^[15]和侧支循环的位置^[16]。

2 溶栓治疗的方法

静脉溶栓是当代临床较为广泛的溶栓方法,它通过静脉的方式将溶栓剂注入体内,从而达到治疗的目的。根据卒中早期治疗指南,一般使用剂量为 0.9 mg/kg,最大量为 90 mg,快速静脉推注总量的 10%,剩余部分在 60 分钟静脉滴注完毕。而 "日本急性卒中溶栓登记研究" 报道使用剂量为 0.6 mg/kg,认为此剂量具有安全性及有效性^[17]。静脉溶栓具有很多优点,例如:操作方法简单,病房可直接操作;对患者造成的创伤较小;同时可在短时间内完成;医疗费用较低。但是,当使用药物剂量过大时,就会影响人体的纤溶系统,增加出血的机率;对于发病 >6 h 的脑梗死患者,疗效较差,出血机率也增加^[18]。

3 溶栓治疗的药物

当今溶栓药物种类繁多,其中我国最常用的是尿激酶(UK)与重组组织型纤溶酶原激活剂(rt-PA),以下将详细介绍 UK 及 rt-PA。

尿激酶(UK)为第一代溶栓药物,它是从健康人体尿液中分离的一种酶蛋白,直接作用于内源性纤维蛋白溶解系统,通过催化纤溶酶原使之成为纤溶酶,进而发挥溶栓作用。我国 "九五" 攻关课题试验研究结果显示 6 小时内给予 UK 100 万 ~ 150 万 IU 进行溶栓治疗,取得了良好的治疗效果。由于 UK 溶栓效果较好,价格相对便宜,因此在临床上被广泛使用,尤其是在中小型医院,使得更多的 AIS 患者受益。但是 UK 是非选择性溶酶激活剂,有激活全身血循环中的纤溶酶原的可能,极易出现溶栓后出血,因此在医院治疗上受到限制。

阿替普酶(rt-PA)为第二代溶栓药物,它是一种糖蛋白,是由血管的内皮细胞所产生的,它可以激活纤溶酶原,促进纤维蛋白的降解。它是选择性纤溶酶原激活剂,与纤维蛋白有较强的亲和力,能特异性的激活血栓中的纤溶酶原,而不引起系统性纤溶状态,因而不容易出现出血倾向。目前,rt-PA 已经成为欧洲和美国脑梗死诊疗指南的推荐用药,是临床上应用较多、相对理想的溶栓药物之一。我国 "十一五" 规划的调查表明,只有 16 % 的 AIS 患者在发病 3 小时内到达医院,其中接受 rt-PA 溶栓治疗的患者为 1.3 %。国内患者对疾病的认识程度及医疗资源的限制,就诊时间延长等因素造成了治疗率的下降。据统计患者就诊时间约为 115 分钟,从完成 CT 检查到使用 rt-PA 溶栓治疗的时间大概需要 86 分钟,其中只有 7 % 的患者就诊时间低于 60 分钟,而美国可达到 27 %^[19,20]。rt-PA 的溶栓效果优于 UK,但是价格昂贵,溶栓时间窗限制,目前很难在中小型医院普及。

4 预后的可能影响因素

4.1 溶栓前 NIHSS 评分

正如一些研究显示,溶栓患者的预后严重性主要是对神经功能恢复的程度和死亡风险的预测评估。Demchuk 等^[21]随机从美国、加拿大和德国 AIS 患者中抽取 1205 人进行 IV rt-PA 溶栓治疗,试验研究表明患者既往基础疾病越少,NIHSS 评分越低,预后越好。他们还指出,患者临床症状越重(如患者处于昏

迷或者是意识模糊状态),预后效果越差。Dharmasaroja 等人^[22]收入 203 例患者进行观察性研究,其结果显示:NIHSS 评分平均数为 8 的患者预后良好,而平均 NIHSS 评分平均数为 15 的患者预后不佳,通过逻辑回归分析结果得出:溶栓前 NIHSS 评分越低,AIS 患者溶栓治疗后预后越好。

4.2 溶栓前血糖

研究表明,AIS 患者发病时血糖越高,其预后越差和 3 个月的死亡率越高^[23]。加拿大学者对 1098 例 AIS 患者接受 rt-PA 溶栓治疗进行观察研究,发现 AIS 患者发作时血糖高,死亡的风险、症状性颅内出血概率较高及 90 天的功能性恢复预后较差^[24]。Ribo 等人^[25]使用 TCD 技术对接受溶栓治疗的 139 例患者进行评估,观察其溶栓后 2 小时阻塞的血管是否可以再通,研究发现溶栓前血糖高于 15.8 mg/L 的患者再通率较低,通过逻辑回归分析显示,溶栓前血糖偏低,AIS 患者溶栓治疗后预后越好。

4.3 溶栓前血压

Ahmed 等人^[26]从 11080 例接收的 rt-PA 的溶栓治疗的患者研究得出以下结论:溶栓 24 小时内血压较高的患者,预后欠佳;血压与症状性颅内出血成线性关系,而血压与预后呈 U 形曲线关系,患者的收缩压血压介于 141-150 mmHg 时,预后最佳。在 ECASSI 数据中,学者分析发现:溶栓期间血压升高与不良预后密切相关,通过逻辑回归分析结果显示,溶栓前收缩压较低的 AIS 患者,溶栓治疗后预后越好。

4.4 既往有无糖尿病病史

一些学者对 NINDS 研究分析发现既往有糖尿病的 AIS 患者溶栓治疗后,3 个月的临床功能恢复欠佳。Faivre 等人^[27]对溶栓治疗的 101 例法国的 AIS 患者进行分析,得出有无糖尿病是一个独立的预测因素,无糖尿病与溶栓后预后良好密切相关。Zangerle 等人^[28]使用一些技术(如 CT 血管造影术,CT 灌注成像扫描仪和 TCD)进行研究,检查 64 例已接受溶栓的患者血管再通状况,其显示糖尿病组与非糖尿病组完全再通率分别为 9.1 % 和 66.0 %,通过逻辑回归分析表明,既往无糖尿病病史的 AIS 患者,溶栓后预后越好。

4.5 脑白质疏松症

一些研究发现,脑白质疏松症是一个独立的因素,它可能影响 rt-PA 溶栓治疗的预后。更重要的是,患者存在脑白质疏松症,溶栓后预后较差。然而只有 Jung 等人^[29]在研究中发现动脉内溶栓的患者,如果存在脑白质疏松症,其溶栓后预后欠佳。有些学者^[30]认为脑白质疏松症的发生与大脑缺氧、缺血,血脑屏障和血流动力学改变有关,它们能导致的衰老,高血压,糖尿病,卒中,高血脂等,影响了溶栓治疗的预后,此种情况使用溶栓剂可能会增加颅内出血风险,老年人也不例外。

除了上面所讨论的这些因素,其他因素可能影响溶栓的结果包括缺血性脑卒中的亚型^[31],性别^[32],房颤^[33],短暂性脑缺血发作^[34],动脉粥样硬化,吸烟^[35],使用降脂药物^[36]和抗血小板聚集药物^[37],卒中发作时大脑中动脉闭塞^[38],这些在治疗时都必须注意。

5 展望

"时间就是大脑",在溶栓时间窗内,越早使用溶栓药物,患者的受益程度就越大。因此,各级医院都应该大力宣传急性

缺血性脑梗死的危害,加强公众的预防意识,积极控制疾病的相关危险因素。由于溶栓时间窗较短,患者的就诊意识较差,医疗人力资源缺乏,导致很多患者未能及时治疗,耽误了病情。因此,可以尝试在各个医院组建急性脑梗死治疗的绿色通道,缩短就诊时间,争取在4.5小时内使用rt-PA溶栓治疗;再者需要培养大量的优秀神经科医生,灵活把握溶栓时间窗和溶栓药物的剂量,进行个体化治疗。相信通过广大科研工作者、神经科医生和全社会的共同努力,一定会使更多的脑梗死患者有机会进行溶栓治疗,使他们受益。

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