

•临床研究 Clinical research•

介入溶栓与静脉溶栓治疗肺栓塞有效性和安全性 Meta 分析

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【摘要】目的 采用 Meta 分析对比介入溶栓与静脉溶栓治疗肺栓塞的效果和安全性。**方法** 检索数据库 PubMed、Embase、Web of Science、Cochrane Library、Clinical Trials, 中国知网、维普、万方及中国生物医学文献服务系统(SinoMed)中对比介入溶栓与静脉溶栓治疗肺栓塞效果和安全性的相关文献, 检索日期为建库至 2021 年 8 月。根据纳入和排除标准筛选文献。采用 RevMan 5.3 和 Stata 14.0 软件分析介入溶栓与静脉溶栓治疗肺栓塞住院期间病死率、颅内出血发生率及大出血发生率比值比(OR)和 95%CI, 并对文献发表偏倚进行分析。**结果** 共有 7 篇文献 66 267 例肺栓塞患者纳入研究。其中 12 269 例接受介入溶栓治疗(介入溶栓组), 53 998 例接受静脉溶栓治疗(静脉溶栓组)。Meta 分析结果显示, 介入溶栓组患者住院期间病死率[OR=0.35, 95%CI(0.28, 0.43), $P<0.01$]、颅内出血发生率[OR=0.62, 95%CI(0.45, 0.85), $P=0.003$]低于静脉溶栓组, 差异均有统计学意义; 大出血发生率低于静脉溶栓组, 但差异无统计学意义[OR=0.74, 95%CI(0.50, 1.11), $P=0.15$]。对住院期间病死率进行发表偏倚分析, 漏斗图显示两侧基本对称, Egger 检验提示文献存在发表偏倚可能性小($P=0.627$)。**结论** 介入溶栓治疗肺栓塞效果和安全性优于静脉溶栓, 住院期间病死率和颅内出血发生率较低。

【关键词】 肺栓塞; 溶栓; 介入治疗; Meta 分析

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Interventional thrombolysis versus intravenous thrombolysis for the treatment of pulmonary embolism: a meta-analysis of efficacy and safety WANG Haijun, YANG Wangjiao. Department of Respiratory Medicine, Dongyang People's Hospital, Jinhua, Zhejiang Province 322100, China

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【Abstract】 Objective To compare the efficacy and safety of interventional thrombolysis and intravenous thrombolysis in the treatment of pulmonary embolism by using meta-analysis. **Methods** A computerized retrieval of academic papers concerning the relevant study comparing the efficacy and safety between interventional thrombolysis and intravenous thrombolysis for pulmonary embolism from PubMed, Embase, Web of Science, Cochrane Library, Clinical Trials, CNKI, VIP, Wanfang database and China Biomedical Literature Service System (SinoMed) was conducted. The retrieval period was from the establishment of the database to August 2021. The academic papers were screened according to inclusion and exclusion criteria. RevMan 5.3, Stata14.0 software were used to compare the odds ratio (OR) and 95%CI of in-hospital mortality, incidence of intracranial hemorrhage and incidence of massive hemorrhage between interventional thrombolysis therapy and intravenous thrombolysis therapy for pulmonary embolism. And the publication bias of the academic papers was analyzed. **Results** A total of 7 papers including 66 267 patients with pulmonary embolism were enrolled in this study. Of the 66 267 patients, 12 269 patients received interventional thrombolysis (interventional thrombolysis group) and 53 998 patients received intravenous thrombolysis (intravenous thrombolysis group). Meta-analysis results showed that the in-hospital mortality (OR=0.35, 95%CI=0.28-0.43, $P<0.01$) and incidence of intracranial hemorrhage (OR=0.62, 95%CI=0.45-0.85, $P=0.003$) in the interventional thrombolysis group were remarkably lower than those in the intravenous thrombolysis group, the differences were statistically significant; the incidence of massive

hemorrhage in the interventional thrombolysis group was lower than that in the intravenous thrombolysis group, but the difference between the two groups was not statistically significant ($OR=0.74$, $95\%CI=0.50-1.11$, $P=0.15$). Publication bias analysis for in-hospital mortality showed that the two sides of funnel diagram were basically symmetrical, and Egger's test suggested that there was less possibility of publication bias ($P=0.627$).

Conclusion In treating pulmonary embolism, interventional thrombolysis is superior to intravenous thrombolysis in clinical safety, in-hospital mortality and incidence of intracranial hemorrhage.

【Key words】 pulmonary embolism; thrombolysis; interventional therapy; meta analysis

肺栓塞致死率高,治疗策略主要是静脉溶栓和抗凝治疗,静脉溶栓与抗凝治疗相比可降低病死率及复发风险,但显著增加大出血和颅内出血风险^[1-2]。随着介入治疗技术发展,介入溶栓为肺栓塞治疗提供了新方法,具有安全性高、改善症状迅速等优点。本研究通过 Meta 分析方法评价介入溶栓与静脉溶栓治疗肺栓塞的有效性和安全性,为肺栓塞治疗决策提供参考。

1 材料与方法

1.1 文献检索

检索数据库 PubMed、Embase、Web of Science、Cochrane Library、Clinical Trials, 中国知网、维普、万方及中国生物医学文献服务系统(SinoMed), 检索日期为建库至 2021 年 8 月。中文检索词:“肺栓塞”“介入溶栓”“静脉溶栓”;英文检索词:“pulmonary embolisms”“embolism, pulmonary”“embolisms, pulmonary”“pulmonary thromboembolisms”“pulmonary thromboembolism”“thromboembolism, pulmonary”“thromboembolisms, pulmonary”“system thrombolysis”“intravenous thrombolysis”“catheter thrombolysis”。

1.2 文献纳入和排除标准

纳入标准:①对比介入溶栓与静脉溶栓治疗肺栓塞疗效和安全性;②观察指标为住院期间病死率、颅内出血率、大出血率。排除标准:①非中文或英文文献、重复发表文献;②文献数据信息不全或无法获取有效结局数据;③干预措施仅为介入治疗,无局部溶栓治疗;④文献类型为动物实验、药物代谢动力学研究、方法学研究和综述等。

1.3 数据提取与文献质量评价

由 2 名研究人员独立检索、筛选文献并提取数据,有分歧时经讨论决定。提取资料包括:第一作者、发表年份、研究类型、样本量、受试者年龄、观察指标(住院期间病死率、颅内出血率、大出血率)。采用 Newcastle-Ottawa 量表(NOS)对纳入文献质量进行评价,包括病例选择、组间可比性、结果等 3 个

项目,满分为 9 星,5 星及以上为高质量文献。

1.4 统计学分析

采用 RevMan 5.3 和 Stata 14.0 软件进行统计学分析。采用 I^2 和 Q 检验进行异质性检验,各研究间无异质性用固定效应模型,否则用随机效应模型。计数资料以比值比(OR)为效应指标,各效应量以 $95\%CI$ 表示。绘制漏斗图评估发表偏倚,行 Egger 检验。 $P<0.05$ 为差异有统计学意义。

2 结果

共检索到 1 507 篇相关文献。根据纳入和排除标准剔除重复文献后获得 1 116 篇,排除综述、系统评价、Meta 分析、动物实验文献后初筛得到 883 篇;阅读文献摘要、排除研究内容不吻合后获取全文文献 44 篇;阅读全文排除研究内容不吻合、结局指标不吻合、研究设计不吻合和无法获取有效信息文献后,最终有 7 篇文献^[3-9]66 267 例肺栓塞患者纳入研究。其中 12 269 例接受介入溶栓治疗(介入溶栓组),53 998 例接受静脉溶栓治疗(静脉溶栓组)。纳入文献 NOS 评分均为 6 星以上,提示文献质量高。纳入文献基本特征及质量评价结果见表 1。

7 项研究^[3-9]住院期间病死率间异质性检验为 $I^2=80\%$, Q 检验 $P<0.01$,提示各研究间存在异质性,故行随机效应模型分析;结果显示介入溶栓组住院期间病死率低于静脉溶栓组 [$OR=0.35$, $95\%CI(0.28, 0.43)$, $P<0.01$],见图 1。7 项研究中 6 项^[3-8]颅内出血发生率间无明显异质性($I^2=0\%$, $P=0.42$),故行固定效应模型分析;结果显示介入溶栓组颅内出血发生率低于静脉溶栓组 [$OR=0.62$, $95\%CI(0.45, 0.85)$, $P=0.003$],见图 2。7 项研究中 3 项^[4, 6-7]大出血发生率间存在异质性($I^2=89\%$, $P=0.01$),结果显示介入溶栓组与静脉溶栓组大出血发生率差异无统计学意义 [$OR=0.74$, $95\%CI(0.50, 1.11)$, $P=0.15$],见图 3。对 7 项研究住院期间病死率进行发表偏倚分析,漏斗图显示两侧基本对称(图 4),Egger 检验提示文献存在发表偏倚可能性小($P=0.627$)。

表1 7篇纳入文献基本特征及文献质量评价

作者	年份	研究类型	研究对象(n)		年龄(岁)		男性(例)		休克(%)		质量评价
			介入溶栓组	静脉溶栓组	介入溶栓组	静脉溶栓组	介入溶栓组	静脉溶栓组	介入溶栓组	静脉溶栓组	
Arora等 ^[3]	2017	回顾性	1 128	2 256	—	—	593	1 170	6.1	10.0	6星
Beyer等 ^[4]	2020	回顾性	2 060	3 376	60.0±15.2	59.2±15.9	1 045	1 724	6.9	15.8	7星
Geller等 ^[5]	2020	回顾性	629	629	57.3±16.3	57.5±16.6	343	345	5.4	4.6	6星
Hobohm等 ^[6]	2021	回顾性	1 175	40 728	68(53,76)	69(57,77)	573	19 357	13.2	20.7	7星
Lin等 ^[7]	2021	前瞻性	145	1 158	63.4±16.5	62.8±15.7	56	527	36.0	37.9	8星
Patel等 ^[8]	2015	回顾性	217	651	58(47,69)	58(47,70)	80	241	20.3	21.2	6星
Stein等 ^[9]	2021	回顾性	6 915	5 200	60.0±15.0	59.0±16.0	46	47	—	—	7星

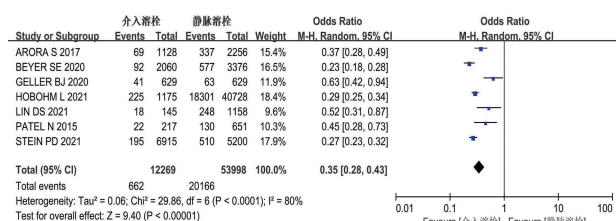


图1 介入溶栓组与静脉溶栓组间住院期间病死率Meta分析森林图

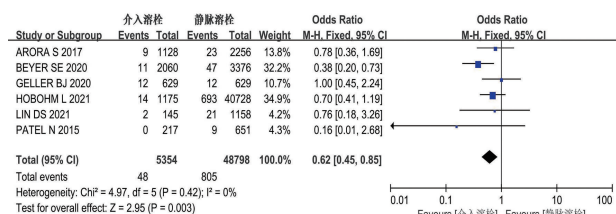


图2 介入溶栓组与静脉溶栓组间住院期间颅内出血发生率Meta分析森林图

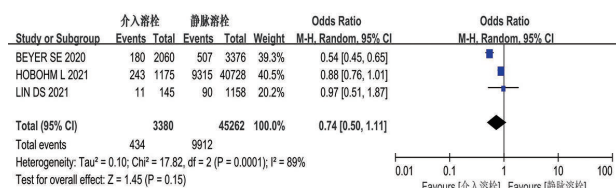


图3 介入溶栓组与静脉溶栓组间住院期间大出血发生率Meta分析森林图

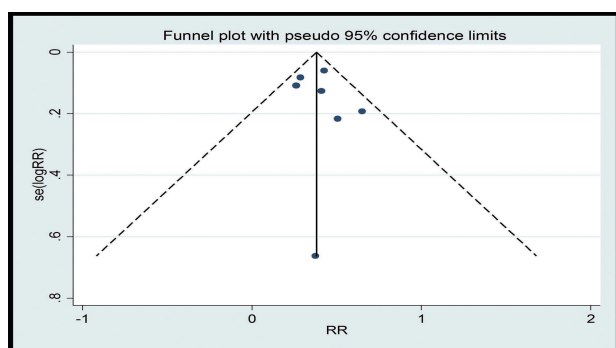


图4 住院期间病死率发表偏倚分析漏斗图

3 讨论

肺栓塞时栓子阻塞肺动脉,肺动脉阻力增加,导致肺动脉压力升高、右心功能不全,从而出现血流动力学不稳定、呼吸功能不全。静脉溶栓是高危肺栓塞首选治疗方法,可降低住院期间病死率,尤其是对于有休克或需呼吸机辅助呼吸的不稳定肺栓塞,但由于出血风险高,仅30%不稳定肺栓塞患者接受静脉溶栓^[10]。相比静脉溶栓,介入溶栓可机械疏通血管,恢复部分血流,较快改善患者临床症状,具有较好的血栓清除率,溶栓效果较优^[11-12]。介入溶栓是通过溶栓导管将溶栓药物直接注入血栓处,可提高血栓处血药浓度,且碎栓后可增加溶栓药物与血栓接触面积,溶栓药物剂量低。有研究表明,介入溶栓治疗高危和中危肺栓塞具有较高的临床成功率^[13]。一项Meta分析显示介入溶栓治疗大面积和次大面积肺栓塞后颅内出血发生率为0.35%,而致命的颅内、眼内或腹膜后出血或任何需要输血或手术修复的明显出血在内的主要并发症发生率为4.65%,大部分仅需输血改善症状^[14]。目前介入溶栓治疗肺栓塞是否优于静脉溶栓尚无定论。

本研究结果显示,介入溶栓组与静脉溶栓组间住院期间病死率、颅内出血发生率差异均有统计学意义,大出血发生率差异无统计学意义。纳入7篇文献间存在异质性,考虑与介入溶栓治疗的药物不同、药物剂量不一致及是否采用超声辅助溶栓治疗有关。Beyer等^[4]、Hobohm等^[6]研究显示超声辅助介入溶栓与单纯介入溶栓治疗后住院期间病死率差异无统计学意义。Lin等^[7]发现,介入溶栓组肺栓塞治愈后1年内复发率显著低于静脉溶栓组,两组间新发肺动脉高压的差异无统计学意义。Geller等^[5]研究结果显示,介入溶栓治疗肺栓塞消化道出血率高于静脉溶栓。目前关于肺动脉高压、肺栓塞复发率及消化道出血研究报道尚不多,仍需更多临床研究进一步证实。

《肺血栓栓塞症诊治与预防指南》^[15]推荐对高危肺栓塞或临床恶化的中危肺栓塞患者行介入治疗,认为静脉溶栓出血风险高患者接受介入溶栓治疗较优于静脉溶栓。一项多中心回顾性研究显示,介入溶栓治疗中危肺栓塞后 1 年全因死亡率明显低于低剂量静脉溶栓治疗^[16]。超声辅助介入溶栓治疗存在至少一个出血危险因素的中危肺栓塞后患者 30 d 全因死亡率显著低于传统抗凝治疗、静脉溶栓治疗^[17]。与标准抗凝治疗相比,介入溶栓治疗入住重症监护病房的急性中危肺栓塞后患者 30 d、1 年死亡率均降低,大出血发生率未增加^[18]。Geller 等^[5]研究也显示介入溶栓治疗肺栓塞后患者 30 d 死亡率明显低于静脉溶栓治疗。

本研究局限性:①由于检索所录中文文献不符合纳入标准,纳入文献均为英文文献;②原文献中介入溶栓治疗药物及剂量未具体说明,治疗效果和安全性分析可能存在偏差;③文献多数为回顾性研究,非随机对照试验。本研究结论有待增加高质量、多中心随机对照研究进一步验证。

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