

Mechanism of gelatin sponge-hemagglutinin blocking agent used in pig lung puncture biopsy

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[Abstract] **Objective** To observe the pathological changes of gelatin sponge-hemagglutinin blocking agent after percutaneous lung puncture, and to explore its mechanism of preventing postoperative complications. **Methods** Totally 12 Bama miniature pigs underwent CT-guided percutaneous lung biopsy. Gelfoam-hemocoagulase mixture were injected into the cutting area of snapping, and the puncture needle passage was blocked at the same time. Chest CT scan was performed for 3 pigs 1, 4, 8 and 12 days after operation, respectively. The sizes of gelfoam-hemocoagulase mixture were observed and recorded. The animals were sacrificed 1 day after CT scan. The lung tissue containing gelfoam-hemocoagulase mixture were obtained, and routine HE staining was performed to observe the pathological changes of gelfoam-hemocoagulase mixture and surrounding lung histopathology under the microscopy. **Results** CT showed that the maximum diameters of gelfoam-hemocoagulase mixture was (14.45 ± 1.43) mm, (9.79 ± 1.80) mm and (3.09 ± 1.04) mm 1, 4 and 8 days after operation ($P < 0.01$), respectively. Gelfoam-hemocoagulase mixture were almost absorbed 12 days after operation. Gelfoam-hemocoagulase mixture in lung tissue were round or oval 1 day after operation, red blood cell infiltration and thrombosis could be seen in the space, the surrounding lung tissues were compressed, and the mud strips completely blocked the needle path. Four days after operation, gelfoams were observed in all samples in form of blood and gelatin sponge mixture, gelatin sponge particles were mostly fused, and the internal space was reduced. The structure of gelfoam-hemocoagulase mixture was loose and the space enlarged 8 days after operation. Twelve days after operation, only residual gelfoam area was observed, no mixture was found, and the lung tissue around the mud was slightly fibrotic. **Conclusion** Gelfoam-hemocoagulase mixture given after CT-guided percutaneous lung biopsy of pigs could exert the effect of hemostasis and prevention of pneumothorax by absorbing blood and pressing lung tissue, which could be completely absorbed within body and therefore being rather safety.

[Keywords] lung; biopsy, needle; gelatin sponge, absorbable; snake venom hemagglutinin; swine

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明胶海绵-血凝酶封堵剂用于猪肺穿刺 活检的作用机制

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[摘要] **目的** 观察经皮肺穿刺后给予明胶海绵-血凝酶封堵剂所致病理学变化, 探讨其预防术后并发症的作用机制。**方法** 对 12 头巴马小型猪行 CT 引导下经皮肺穿刺, 于肺内活检针切割区注入明胶海绵-血凝酶封堵剂泥浆, 并封堵穿刺针道。分别于术后 1、4、8 和 12 天各对 3 头猪行胸部 CT 扫描, 观察明胶海绵泥浆球变化; CT 扫描后 1 天处死动物, 获取包含明胶海绵的肺组织, 行常规 HE 染色后, 于光镜下观察明胶海绵和周围肺组织病理学改变。**结果** 经皮肺穿刺术后 1、4、8 天, 活检针切割区明胶海绵泥浆球最大径分别为 (14.45 ± 1.43) mm、 (9.79 ± 1.80) mm 和 (3.09 ± 1.04) mm ($P < 0.01$), 术后 12 天明胶海绵基本被吸收。术后 1 天肺组织中的明胶海绵泥浆球呈圆形或椭圆形, 间隙内可见红细胞浸润和血栓形成, 周围肺组织受明胶海绵泥浆压迫, 针道完全被封堵剂泥浆条封堵; 术后 4 天明胶海绵泥浆均以血液和明胶海绵混合物形式存在, 明胶海绵颗粒大部分融合, 其内部空间减小; 术后 8 天明胶海绵结构松散, 间隙增大; 术后 12 天仅见残留明胶海绵泥浆区域, 无混合物, 泥浆周围肺组织少量纤维化。**结论** CT 引导下经皮肺活检后给予明胶海绵封堵剂可通过吸收血液、压迫肺组织而达到止血和预防气胸的效果; 且封堵剂在体内可完全吸收, 安全性好。

[关键词] 肺; 活组织检查, 针吸; 明胶海绵, 吸收性; 蛇毒血凝酶; 猪

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CT 引导下经皮肺活检已广泛应用于肺部占位性病变诊断, 其总体阳性率达 $92.0\% \sim 98.2\%$ ^[1], 但术后常见气胸、肺出血及空气栓塞等并发症^[2-5]。既往研究^[5-8]报道, 明胶海绵颗粒可应用于封堵穿刺道或活检切割区, 以预防气胸等并发症。但关于肺内直接注射明胶海绵尚无明确共识或指南, 其注射到肺内的安全性和有效性亦少见报道。本课题组将明胶海绵混合物与蛇毒血凝酶混合制备明胶海绵-血凝酶封堵剂。本研究观察经皮肺穿刺后给予的明胶海绵-血凝酶封堵剂的病理学变化, 分析其预防穿刺后出血、气胸的作用机制。

1 材料与方法

1.1 实验动物 选取体质量 $20 \sim 25$ kg 的巴马小型猪 12 头, 雌雄不限, 购自北京实创实验动物公司(动物许可证编号: 2019-D15-07)。本研究获中国人民解放军总医院第一医学中心实验动物伦理委员会批准。

1.2 仪器与方法 采用 Philips Brilliance 多排螺旋 CT 扫描仪, 定位栅引导, 对小型猪行经皮肺穿刺, CT

扫描层厚 5 mm, FOV 512×512 , 管电压 120 kV, 管电流 305 mAs。

术前给予动物咪达唑仑 (0.5 mg/kg 体质量) 和盐酸赛拉嗪 (20 mg/kg 体质量) 肌肉注射以镇静, 而后经耳缘静脉泵入丙泊酚 [0.40 mg/(kg · h)] 维持镇静。采用利多卡因 (0.1 g) 对 CT 规划的进针点进行局部浸润麻醉至胸膜。将 18G 同轴穿刺针 (TSK Surecut) 刺入肺野外带距胸膜 $1 \sim 2$ cm 处, 并以活检枪取肺组织标本。而后拔出针芯, 将装有明胶海绵-血凝酶封堵剂泥浆 (以下简称明胶海绵泥浆) 的注射器与引导针外套管连接, 将明胶海绵泥浆注入肺内, 对每头猪于每侧肺不同位置分别进行 4 次以上操作, 而后将引导针拔出。

明胶海绵-血凝酶封堵剂泥浆配制及注射方法: 拔出 2 ml 注射器的活塞, 打开装有明胶海绵颗粒 (100 mg, $560 \sim 710$ μ m) 的西林瓶, 将注射器末端与西林瓶口吻合, 将明胶海绵颗粒倒入 2 ml 注射器中, 将活塞推回注射器, 压缩明胶海绵并排出空气; 以注射器

针头抽吸蛇毒血凝酶(1 ml),使明胶海绵与血凝酶混合后配制泥浆;配置时间约 1 min。注射泥浆时保持针鞘位置稳定,通过针鞘将泥浆注入肺内,直到注射完毕或出现较大阻力,此时肺内活检针切割区产生 1 个明胶海绵泥浆球;拔出注射器,并将针芯推入针鞘内约 2~3 cm,针芯位置稳定后将针鞘向后抽出,直到其脱离



图 1 明胶海绵泥浆球(上)及泥浆条(下)实物图

皮肤,最终在针道内留下 1 条明胶海绵泥浆条(图 1)。

1.3 相关指标观察 分别于术后 1、4、8 和 12 天各对 3 头猪行胸部 CT 扫描,测量明胶海绵泥浆球最大径。CT 扫描后 1 天注射戊巴比妥钠(200 mg/kg 体重)处死动物,获取包含明胶海绵泥浆球及泥浆条的肺组织(肺组织超过明胶海绵边缘至少 1 cm),以石蜡包埋后行 5 μ m 厚切片,常规 HE 染色,于光镜下观察明胶海绵和周围肺组织病理学改变。

1.4 统计学分析 采用 GraphPad Prism 8 统计分析软件。以 $\bar{x} \pm s$ 表示符合正态分布且方差齐的计量资料,采用单因素方差分析比较各时间点数据。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 CT 所示明胶海绵泥浆球最大径 CT 图像显示,术后 1、4、8 天,明胶海绵泥浆球最大径分别为 (14.45 ± 1.43) mm、 (9.79 ± 1.80) mm 和 (3.09 ± 1.04) mm,差异有统计学意义($F=359.40, P < 0.01$),见图 2。术后 12 天明胶海绵明显吸收,难以测量明胶海绵泥浆球最大径而无法分析。

2.2 病理学表现 术后 1 天肺组织中明胶海绵泥浆球呈圆形或椭圆形的颗粒状结构。83.33%(20/24)样本中明胶海绵颗粒清晰锐利,间隙内可见红细胞浸润和血栓形成;周围肺组织受明胶海绵泥浆压迫而致肺泡腔消失,细胞紧密相连形成一堵细胞“墙”。针道内充满明胶海绵泥浆和血液混合物,即针道完全被牙膏状明胶海绵泥浆条所封堵。术后 4 天所有样本(24 个)中明胶海绵泥浆均以血液和明胶海绵混合物形式存在,明胶海绵颗粒大部分融合,海绵内部空间减小;周围肺组织与术后 1 天无明显差别,未见炎症反应。术后 8 天所有样本(24 个)中血液和明胶海绵混合物已变为表面光滑的血肿(即部分混合物被吸收),明胶海绵结构松散、间隙增大,周围肺组织中的细胞“墙”随明胶海绵减少而减小,肺组织内未见炎症和肉芽组织,

局部肺泡上皮细胞增生。术后 12 天光镜下仅见残留明胶海绵泥浆区域、无混合物,明胶海绵泥浆周围肺组织少量纤维化,见图 2、3。

3 讨论

气胸、出血为经皮肺穿刺活检术后常见并发症,影响后续治疗及患者预后。本研究以猪为研究对象,模拟临床 CT 引导下经皮肺穿刺活检过程,以明胶海绵泥浆进行局部压迫和针道封堵,并采用 CT 及病理学检查观察泥浆变化。结果提示,将明胶海绵泥浆注入活检切割区和针道内可以吸收血液并有效封堵,达到止血和预防气胸效果;且存留于肺内的明胶海绵可被机体完全吸收,历时约 8~12 天;封堵可引起轻度肺纤维化,但仅限于泥浆周围狭窄边缘,提示其安全性较高。

本研究所用明胶海绵泥浆可达到“双重封堵”效果:①在功能方面,明胶海绵泥浆同时具有止血和密闭双重作用;②空间上能同时封堵切割区和针道;③在止血机制上,明胶海绵和蛇毒血凝酶均具有促凝血功效;④在气密性上,明胶海绵和血凝块二者同时具有封闭作用。同时,明胶海绵泥浆的制备及使用技术至关重要。本研究在术前按规定剂量和方法配制明胶海绵泥浆备用,术中注射入体内的明胶海绵泥浆剂量和体积明确,且形态较为一致。

气胸是 CT 引导下经皮肺活检最常见并发症。既往研究^[4,9-11]表明,病变类型、患者体位、针道长度和病变位置等均与肺穿刺活检后气胸发生率相关,并影响其程度和频率。肺穿刺活检后气胸发生率约 8.4%~53.5%^[12-13],置管引流率最高达 18.6%^[14-15]。CT 引导下经皮肺穿刺活检术中发生气胸的主要原因是空气通过穿刺道从肺部泄漏到胸膜腔,故封堵穿刺道可预防气胸。本研究将明胶海绵泥浆条留置于穿刺通道内,形成 1 条与穿刺道形状完全匹配的“牙膏”状海绵泥浆条,能有效预防肺部空气通过穿刺道进入胸膜腔而引发气胸。

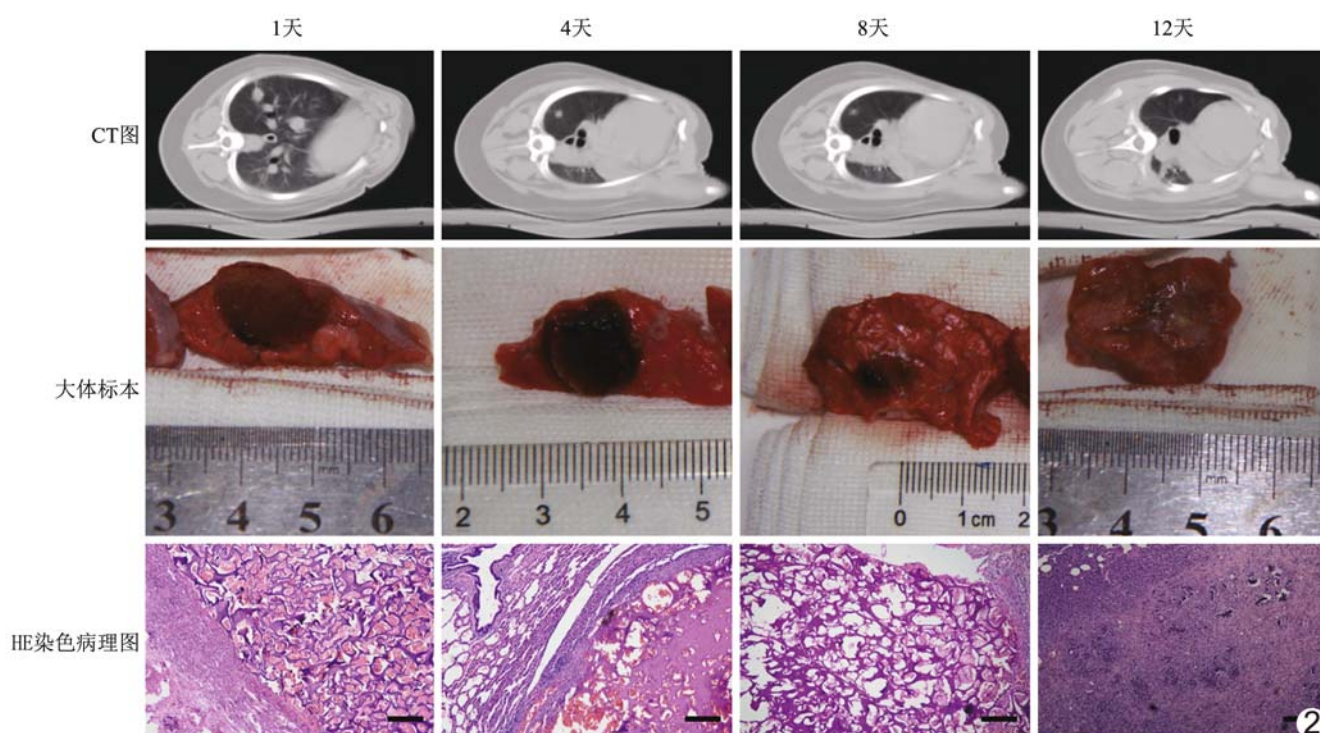


图2 向肺内直接注射后明胶海绵泥漿的动态变化 CT图、大体标本和光镜下观察 HE染色病理图均提示明胶海绵泥漿球体在术后8~12天逐渐被吸收。术中注入肺内的明胶海绵泥漿呈颗粒状结构,边缘清晰;术后1天颗粒清晰;术后4天明胶海绵泥漿体积缩小,颗粒模糊;术后8天明胶海绵泥漿体积减小;术后12天明胶海绵泥漿被基本吸收

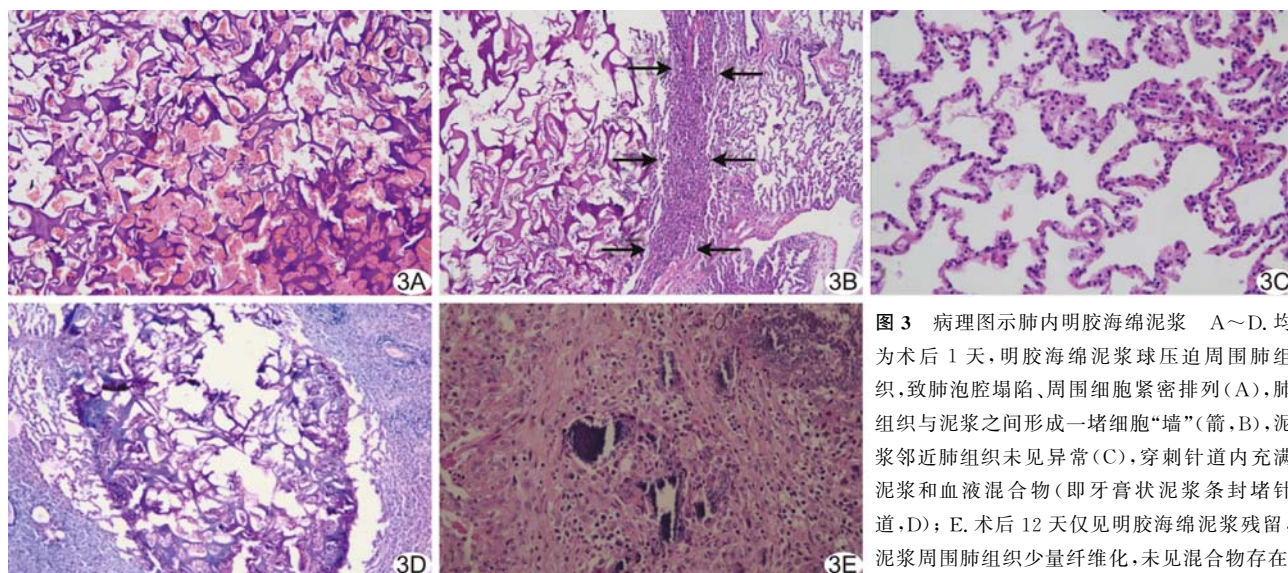


图3 病理图示肺内明胶海绵泥漿 A~D.均为术后1天,明胶海绵泥漿球压迫周围肺组织,致肺泡腔塌陷、周围细胞紧密排列(A),肺组织与泥漿之间形成一堵细胞“墙”(箭,B),泥漿邻近肺组织未见异常(C),穿刺针道内充满泥漿和血液混合物(即牙膏状泥漿条封堵针道,D);E.术后12天仅见明胶海绵泥漿残留,泥漿周围肺组织少量纤维化,未见混合物存在

经皮肺穿刺活检后肺出血发生率为4.3%~53.5%^[16-17],严重者可出现大咯血,导致患者低氧、休克甚至死亡。本研究结果显示明胶海绵泥漿可有效预防肺穿刺后出血,其主要作用机制如下:泥漿球可于活检切割区直接压迫肺组织而发挥止血效果;针道内的明胶海绵泥漿条进一步阻挡血液沿针道流动;被压缩

的肺组织内肺泡腔塌陷,出血难以经肺泡腔扩散;明胶海绵和蛇毒血凝酶本身均具有促进凝血效果。

综上所述,明胶海绵泥漿具有较好的适形性,易于通过同轴针鞘注射,退针后可以很好地与穿刺针道匹配,同时封堵针道和切割区,有效阻止血液和空气经过针道进入胸膜腔而预防气胸、出血,且在体内可被完全

吸收,安全性好。本研究通过动物实验初步探讨明胶海绵泥浆在肺内的病理生理学改变和机制,其有效性和安全性尚需更多临床前研究和临床试验加以证实。

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