

· 综述 ·

英国医学研究委员会脊柱结核多中心随机对照研究系列报道研究进展

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Progress in multicenter randomized controlled trial of spinal tuberculosis in British Medical Research Council

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脊柱结核是最常见的肺外结核之一, 是一类棘手的感染性疾病, 约占骨关节结核的50%~60%^[1]。然而, 关于脊柱结核的治疗理念尤其是手术方式的选择, 国内外存在较大争议。激进或过于保守均会带来各种问题: 手术指征过宽易造成过度治疗, 增加医疗负担甚至各种手术并发症; 手术指征过窄则会导致疗程延长, 继发Pott畸形, 发生迟发性神经损伤等。上述问题的关键在于针对脊柱结核手术及非手术治疗的研究多为病例报道^[2], 高质量随机对照研究较少。英国医学研究委员会(MRC)脊柱结核学组于1965年在亚非等脊柱结核高发生率地区开展了一项除颈椎结核以外的多中心、前瞻性临床随机对照研究, 旨在解决脊柱结核手术与非手术治疗方案的选择^[3]。该研究随访时间长、观察指标全、设计完善, 在随后长达40年(1973~2013)的随访观察中, 比较了早期无严重并发症的脊柱结核患者手术和非手术治疗、短程和长程药物治疗、单纯病灶清除术和病灶清除并结构性植骨融合术的临床疗效, 系列研究结果^[4-16](13篇文献, 630例病例)在*J Bone Joint Surg Br*、*Tubercle*、*Int Orthop*等期刊发表, 研究报道范围如下。①药物治疗: 短程方案(6个月、9个月)和长程方案(18个月)疗效的比较;

②住院和门诊药物治疗、门诊药物治疗是否佩戴石膏支具治疗效果的比较; ③药物治疗、药物治疗并单纯病灶清除术、药物治疗并病灶清除及结构性植骨术等治疗方案在减少后凸畸形、椎体骨质丢失及提高融合率方面的比较。

MRC的系列试验无论是研究设计还是结论评价, 都是脊柱结核领域的一项经典研究, 其诸多研究结果对当下脊柱结核的治疗理念和手术方式均具有重要的指导作用, 本文针对该研究的系列报道进行分析总结, 综述如下。

1 试验研究分组

亚非地区研究组: ①韩国(350例)^[4-9], 分为药物治疗(265例)、住院(83例)和门诊药物治疗(83例)、石膏支具(63例)和非石膏支具(70例); ②中国香港地区(150例)^[10-14], 药物治疗并单纯病灶清除、药物治疗并病灶清除及结构性植骨融合术; ③津巴布韦(130例)^[15-16], 药物治疗并单纯病灶清除术。所有患者分别于术后3、5、10、15年进行随访。

病例纳入标准^[4]: 临床或影像学证据证实T₁~S₁节段活动性椎体结核病变。排除标准: ①严重的神经功能症状、无辅助条件下步行<4 m; ②严重影响治疗效果的其他脊柱外科疾病; ③既往抗结核药物

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治疗 ≥ 12 个月,或者纳入研究前3个月接受过抗结核药物治疗;④既往有脊柱手术史。

评价标准^[4]:①临床症状评价(腰背痛、神经功能损伤、身体活动受限、脓肿和窦道形成);②细菌学评价(血液结核分枝杆菌培养和手术切除病变组织培养);③影像学评价(后凸角度、椎体骨质丢失、椎体融合情况以及病变节段活动度)。治疗有效:临床症状完全缓解,细菌培养阴性及影像学指标证实无活动性病灶。不确定:影像学指标证实无活动性病灶,但临床症状部分改善或者持续活动受限。无效:临床症状持续存在,窦道脓肿形成需额外手术或者改变治疗方案。

药物治疗方案及用量^[4]:①异烟肼(H, 6 mg/kg, 最大剂量300 mg)+利福平(R, 15 mg/kg, 最大剂量600 mg)治疗6个月(6HR方案);②H+R治疗9个月(9HR方案);③H+对氨基水杨酸(P, 0.2 g/kg, 最大剂量10 g)治疗9个月(9PH方案);④H+乙胺丁醇(E, 15~20 mg/kg, 根据年龄,年龄越低剂量相对越高)治疗9个月(9EH方案);⑤H+P治疗18个月(18PH方案);⑥H+E治疗18个月(18EH方案)。

手术治疗方案^[10-13]:①单纯病灶清除术(经胸廓或者腹膜外入路开放清创,将脓肿、死骨和椎间盘碎片彻底清除,对神经组织彻底减压,但不进行植骨);②病灶清除并结构性植骨融合术(改良的Hodgson术式^[17],在病灶清除术的基础上采取自体肋骨、髂骨或者腓骨植骨)。

2 MRC系列研究结果

2.1 不同药物治疗方案

韩国研究小组对于不同的药物治疗方案进行了对比研究^[46]。经过筛选,共纳入病例265例,研究时间为3年。结果发现9PH和9EH、18PH和18EH方案治疗结果相同,最后将其合并为9P/EH、18P/EH一并进行研究。其中短程(6HR 65例、9HR 71例、9P/EH 62例)198例、长程(18P/EH)67例。随访发现短程和长程药物治疗方案的骨质融合、后凸畸形及脊髓病变的发生率差异无统计学意义,但9P/EH方案的窦道、脓肿更容易复发,显著高于6HR和9HR方案(14%比0)。6HR方案和9P/EH方案的椎体骨质丢失最严重。在治疗无效的病例中,9P/EH方案的患者出现的并发症更多。综上,对于脊柱结核药物治疗应以异烟肼和利福平为主要基础方案,短程方案和长程方案相比,在治愈率方面并没有明显的差异,患者的顺应性较好,经济负担降低,尤其适用于发展中国家脊柱结核的治疗。

2.2 住院和门诊药物治疗、门诊药物治疗是否佩戴石膏支具

韩国研究小组在Masan和Pusan对比了住院和门诊药物治疗的效果^[79],共纳入患者299例。Masan组166例,随机分为住院药物治疗(83例)和门诊药物治疗(83例);Pusan组133例,均为门诊药物治疗,随机分为药物治疗并石膏固定组(63例,石膏背心固定9个月)和单纯门诊药物治疗组(70例,未行石膏固定)。上述2组所有患者随机采用18PH方案或SPH方案(18PH+前3个月同时肌注链霉素)。随访10年发现:269例(90.0%)患者治疗有效;30例(10.0%)患者治疗无效,包括急性脊髓结核死亡1例、截瘫3例、持续脊髓损伤1例、病变持续进展(包括窦道、脓肿形成)10例,还有15例患者虽然临床和影像学指标显示治疗效果良好,但由于脊柱病变接受额外的手术或者更改治疗。125例(41.8%)患者在10年随访中出现1次或多次脓肿和窦道形成,10年后218例(72.9%)患者骨质完全融合,23例(7.7%)患者部分融合,余28例患者失访。研究还发现,无论是住院还是门诊药物治疗,对于脓肿和窦道、神经病变的疗效并没有明显的差别,在远期治愈率方面差异没有统计学意义,且佩戴石膏背心对临床治愈率并没有明显的提高。

2.3 不同方案治疗效果的比较

在韩国、中国香港和罗德西亚(后更名为津巴布韦)的研究中,共纳入病例377例^[10-16],随机接受药物治疗、药物治疗并单纯病灶清除术、药物治疗并病灶清除及结构性植骨融合术。最后根据临床表现和影像学表现评价治疗效果。5、10和15年随访结果显示,3种治疗措施总体有效率为87.1%(328例)。15年随访显示单纯药物治疗患者(236/271, 87.0%)和药物并手术治疗患者(92/106, 86.5%)的临床治愈率(无中枢神经受累、身体活动受限、影像学病变和晚期复发或者迟发性瘫痪)差异无统计学意义。与药物治疗相比,2种手术治疗的融合率更高;与单纯病灶清除术相比,病灶清除术并结构性植骨融合手术的脊柱融合率和后凸畸形改善率更高。后凸畸形丢失率病灶清除术并结构性植骨融合手术明显低于单纯病灶清除术,单纯药物治疗者术后后凸畸形持续进展。且手术治疗和单纯药物治疗相比,可以迅速地缓解背部疼痛,早期控制脓肿及窦道,避免神经功能受损。综上,病灶清除并结构性植骨融合术治疗脊柱结核较单纯药物治疗和单纯病灶清除术在减少后凸畸形进展、缓解疼痛、减少窦道和脓肿、避免神经系统损伤等方面具有明显的优势。

3 结 语

MRC开展的脊柱结核研究是迄今为止随访时间最长的临床试验, 对非手术治疗和手术治疗、不同药物治疗方案、不同手术方式治疗脊柱结核的疗效进行了对比, 证实了非手术治疗(药物治疗、卧床休息、支具)在脓肿和窦道的控制、减少后凸畸形、减少神经功能损伤、避免远期并发症等方面具有一定的意义, 但远期会出现各种并发症, 如后凸畸形、脊柱不稳、迟发性Pott截瘫、后背痛、矢状面失衡等, 这些并发症使再次治疗(手术)风险增加。因此, Cheung等^[18]提出: ①单纯的非手术治疗远期复发率高, 随时间进展会出现一系列并发症。②对脊柱结核的临床随访时间应该更长, 以便能及早采取干预措施, 避免远期并发症。③单纯的药物治疗研究应该注重进一步缩短疗程和放宽化疗间隔, 探索合适的方案。手术治疗在临床治愈率方面与药物治疗并没有太大差异, 但是前路病灶清除并结构性植骨融合术较单纯病灶清除术能够早期迅速改善症状、控制脓肿和窦道形成以及促进早期椎体融合, 避免远期后凸畸形的进展。

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