

三联抗生素糊剂在年轻恒牙牙髓再生中的应用

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[摘要] 近年来,牙髓再生作为年轻恒牙牙髓根尖病变的有效治疗方法获得了学界的肯定,而控制根管感染作为其成功的关键也受到广泛关注。三联抗生素糊剂(triple antibiotic paste,TAP)由甲硝唑、环丙沙星和米诺环素组成,适宜浓度下具有理想的抗菌效果和时间,细胞毒性小,有效促进牙髓组织的保存与再生及牙体硬组织的形成,但也存在牙齿变色、细菌耐药等问题。本文对近年来 TAP 在年轻恒牙牙髓再生治疗中的应用及其特点作一综述。

[关键词] 三联抗生素糊剂 牙髓再生 控制感染 根管消毒

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Application of Triple Antibiotic Paste in Pulp Regeneration of Young Permanent Teeth. XU Jingchen^{1,2,3,4}, HUANG Ruijie^{1,2,3*}. 1. State Key Laboratory of Oral Disease Research, Chengdu 610041, China; 2. National Center for Clinical Medicine of Stomatology Diseases, Chengdu 610041, China; 3. Department of Pediatric Stomatology, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China; 4. Department of Orthodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China.

[Abstract] Pulp regeneration has been admitted as an effective treatment of pulpitis and periapical inflammation of young permanent teeth in recent years. The root canal system and periapical region infection control, the key of successful pulp regeneration, becomes a public concern. Triple antibiotic paste (TAP) contains metronidazole, ciprofloxacin, and minocycline. With the appropriate working concentration and time, it could achieve an ideal bacterial inhibitory effect, sterilize the root canal system, minimize cell toxicity, facilitate pulp tissue conversation and regeneration, and promote the root and related tooth hard tissues development. However, there are also some disadvantages of TAP such as tooth discoloration, drug resistance, and etc. This review would summarize the application and characteristics of TAP in the pulp regeneration of young permanent teeth.

[Key words] triple antibiotic paste pulp regeneration infection control root canal system disinfection

年轻恒牙发生牙髓坏死和根尖周病变时,临床传统采用根尖诱导成形术进行治疗,但这种方法无法保存活髓,将使牙齿在丧失冷热等部分感觉的同时变得脆弱易折^[1]。近年来,以保存活髓为目的的牙髓再生技术,受到广泛关注。牙髓再生可通过两种途径实现^[2,3],一是牙髓血运重建,二是利用组织工程学原理实现牙髓牙本质复合体的再生。无论采用何种方法,控制根管感染都是成功的关键。然而年轻恒牙根尖孔未形成,根管壁薄,故根管预备时主要通过化学方法去除感染物质,根管消毒药物的选择和应用愈加重要^[4]。

三联抗生素糊剂(triple antibiotic paste,TAP)于1996年由 Sato 等首次提出,它含有3种抗生素成分:甲硝唑、环丙沙星和米诺环素^[5]。目前广泛认为感染根管主要为需氧菌和厌氧菌的混合感染,单一抗生素治疗效果不佳,故 TAP 凭借其优秀的抗菌性能、较强的渗透性和较小的刺激性,广泛应用于牙髓再生治疗。

1 TAP 的组成

TAP 是由甲硝唑、环丙沙星、米诺环素和木馏油调制而成的糊剂。其中,甲硝唑属硝基咪唑类药物,对各种 G⁺、G⁻及厌氧菌具有较强的作用,不易产生耐药菌株且与大多数抗生素配伍无禁忌。环丙沙星属第3代喹诺酮药物,抗菌谱广,抗菌活性强且不易产生耐药性,尤其是针对 G⁻菌。米诺环素抗菌作用在四环素类药物中最强,对多数 G⁺菌和 G⁻杆菌有良好的抗菌活性,并具有高效性和长效性。

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2 TAP的作用特点

目前,TAP作为有效的根管消毒药物被广泛应用于牙髓再生的基础及临床研究中,并显示出了如下优点:抗菌性强、渗透性强、作用时间长,同时细胞毒性较小,能够促进牙体硬组织形成和牙根继续发育。

2.1 抗菌活性 TAP抗菌活性强,渗透性好。Adl等^[6]的体外实验发现TAP对粪肠球菌的杀灭能力高于氢氧化钙。Windley等^[5]研究结果表明,TAP的杀菌效果强于1.25%次氯酸钠溶液。Devaraj等^[7]同样发现TAP去除根管壁粪肠球菌生物膜的能力显著强于次氯酸钠溶液与氢氧化钙。Albuquerque等^[8]还发现TAP可完全杀灭根管壁上的内氏放线菌。

2.2 浓度及抗菌时间 TAP的作用时间与其浓度有关。Alyas等^[9]的研究发现,TAP浓度在10 g/L以上时可产生长期抗菌效果。但是Chuensombat等^[10]认为,进行根管消毒的最佳TAP浓度并非10 g/L,而是0.39 g/L,能够在保证抗菌效果的同时减小细胞毒性。此外,使用载药纤维支架能够实现药物缓释,延长抗菌时间。

2.3 促进牙髓再生

2.3.1 细胞毒性 根管消毒药物在发挥抗菌消毒作用同时应具有较小的细胞毒性。TAP的干细胞毒性与其组成成分、药物浓度、作用时间及载体有关。Kamocki等^[11]研究发现,当牙髓干细胞(dental pulp stem cells, DPSCs)仅暴露于环丙沙星或二联抗生素糊剂(double antibiotic paste, DAP)(如环丙沙星、甲硝唑)环境中时,其增殖活性明显降低,而单独暴露于甲硝唑时,则无明显变化。Chuensombat等^[10]的研究结果也表明,米诺环素和环丙沙星均为酸性,不利于干细胞的生长和增殖,而甲硝唑为中性,对干细胞活性无明显影响,3种药物联合使用的细胞毒性强于1种药物单独使用,且细胞毒性随浓度增高而增大^[10,12]。Pankajakshan等^[13]的研究结果表明,TAP载药纤维可以通过缓释药物,降低高浓度TAP的细胞毒性,不影响牙髓干细胞的附着及增殖。因此,调节TAP的pH接近中性或使用载药纤维支架均为保护DPSCs的有效方法。

2.3.2 生物相容性 TAP具有良好的生物相容性。其中,四环素类药物能够抑制胶原酶和基质金属蛋白酶的活性,并促进白细胞介素-10(interleukin-10, IL-10)和抗炎细胞因子的分泌^[14,15];而甲硝唑和环丙沙星能够促进成纤维细胞的生成,因此TAP能够促进牙髓再生及牙根继续发育。Bose等^[16]对比TAP、氢氧化钙和甲醛甲酚发现,TAP组形成牙本质厚度高于后两者,能够促进牙髓-牙本质复合体的发育。Scarpato等^[17]的动物实验结果也表明,TAP能在局限根尖感染的同时,促进根尖部牙骨质类似物沉积,促进根尖发育。

2.4.3 临床疗效 牙髓再生的体外实验及临床病例报告均显示,使用TAP消毒可以促进牙髓再生,获得良好的根尖封闭。Schmoeckel等^[18]对年轻恒牙进行牙髓血运重建术时,使用TAP进行根管消毒,患牙根尖周病变痊愈,根尖获得良好封闭效果。Solomon等^[19]在牙髓再生术中使用TAP进

行根管消毒后引入富血小板血浆(platelet-rich plasma, PRP),18个月后形成良好的根尖封闭效果。但有临床报道显示,患者在应用TAP进行根管消毒后出现疼痛等不良反应,换用氢氧化钙糊剂后不适症状消失^[20,21],分析可能与患者的个人体质等因素有关,需要引起口腔医生的注意。

3 TAP的不足及对策

虽然TAP在牙髓再生中显示出了一些优势,但同时也存在一些不足,主要表现为以下几方面:TAP侵蚀根管壁、牙齿变色、细菌耐药、药物过敏反应。

3.1 破坏牙本质表面 Yassen等^[22]的研究发现,TAP对根管壁粗糙度的影响明显优于次氯酸钠溶液及氢氧化钙。同时也有研究结果表明,与DAP和氢氧化钙相比,TAP显著降低了牙本质表面硬度并造成牙本质表面脱矿^[23]。但有学者提出,通过选择适当浓度的TAP或使用载药支架缓释药物,可以减少根管侵蚀,保护根管。

3.2 牙齿变色 米诺环素可与牙本质中的Ca²⁺螯合生成不溶性复合物,沉积于牙体硬组织导致牙齿变色。Akay等^[24]和Santos等^[25]的实验均发现,TAP较氢氧化钙及DAP能使牙齿染色变深,且颜色改变随时间累积。Porter等^[26]的研究发现,含多西环素的TAP较含米诺环素的TAP导致的牙本质着色浅。因此,Yassen等^[22]提议可用DAP或用其他抗生素如阿莫西林、头孢克洛等代替米诺环素,以减轻牙本质着色;亦可通过酸蚀粘接等方法预先封闭牙本质小管,阻止螯合,防止牙齿着色。

3.3 细菌耐药性及药物过敏反应 根管中微生物种类复杂,若使用TAP浓度过高或时间过长,则可能产生耐药菌株,发生再感染,导致治疗失败。因此细菌培养、药敏试验以及寻找合适的TAP浓度及应用时长对于减少细菌耐药性来说至关重要。Hausermann等^[27]报道,环丙沙星可能导致口腔黏膜水肿。De Paz^[28]和Hoefnagel等^[29]报道,米诺环素可能会引起肺炎、嗜酸性粒细胞增多症等药物过敏反应。甲硝唑则可引起荨麻疹、皮肤瘙痒等。虽然药物过敏反应主要由全身用药引起,局部用药少见,但口腔医生同样应提高警惕,保护患者身心健康。

4 结论及展望

TAP抗菌性强、渗透性好,在适宜浓度下,可获得理想的抗菌效果及较小的细胞毒性,同时有效促进牙髓组织的保存与再生及牙体硬组织的形成。虽然其在应用过程中尚存在一些问题,如牙齿变色、细菌耐药等,但随着科技的进步及各位学者的一致努力,以及改良三联抗生素糊剂、二联抗生素糊剂及载药纤维支架等方法的不断涌现,TAP将会拥有更为广阔的应用前景。

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