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预防双膦酸盐相关性颌骨坏死的研究进展

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摘　要

双膦酸盐类药物较广泛地应用于临床骨质疏松的治疗和癌症患者骨转移的抑制，特别是近年来随着对双膦酸盐类药物副作用的认识进一步增加，双膦酸盐相关性颌骨坏死的严重性也越来越受到人们的重视。但由于目前缺乏明确的治疗措施，因此对于此疾病的预防至关重要。本论文综述了预防药物性颌骨坏死的研究进展，重点关注了策略和前沿领域，旨在提供对该疾病的更深入理解和有效管理的指导。

关键词

双膦酸盐，颌骨坏死，流行病学，发生机制，危险因素，治疗，预防措施

Research Progress in the Prevention of Bisphosphonate-Related Jaw Necrosis

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Abstract

In recent years, there has been growing recognition of the side effects associated with bisphosphonate drugs, which are widely used in the treatment of clinical osteoporosis and the inhibition of bone metastasis in cancer patients. One of the severe side effects is bisphosphonate-related osteonecrosis of the jaw (BRONJ), and its severity has been increasingly emphasized. However, the lack of definitive treatment measures makes prevention of this condition crucial. This paper aims

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to provide a comprehensive review of the research progress in preventing drug-induced osteonecrosis of the jaw, focusing on strategies and emerging areas. The goal is to offer guidance for a deeper understanding and effective management of this condition.

Keywords

Bisphosphonates, Necrosis of Jaw, Epidemiology, Pathogenetic Mechanism, Risk Factors, Treatment, Preventive Measure

1. 药物简介

双膦酸盐类药物(bisphonates, BPs)是一类人工合成的焦磷酸盐类似物，特定的化学结构决定了它们对于骨组织具有高选择性。双膦酸盐可分为两种类：不含氮的双膦酸盐和含氮的双膦酸盐。双膦酸盐与骨表面的羟基磷灰石特异性的结合，通过以下机制[1] ① 直接改变破骨细胞的形态学，从而抑制其功能；② 与骨基质理化结合，直接干扰骨吸收；③ 直接抑制成骨细胞介导的细胞因子如 IL-6、TNF 的产生。从而有效抑制骨吸收，减少骨骼相关事件的发生率和减少恶性肿瘤的骨转移等，因此可被用于治疗骨质疏松、Paget's 病、成骨不全症等疾病，但应用后会出现发热、腹痛、眼部不适、颌骨坏死等不良反应。Marx [2]在 2003 年首次报道双膦酸盐相关颌骨坏死(bisphosphonate-related osteonecrosis of the jaws, BRONJ)。近年，由于出现其他导致颌骨坏死的药物，美国颌面外科医生协会(American Association of Oral and Maxillofacial Surgeons, AAOMS)在 2014 年将此类疾病正式命名为 MRONJ。由药物所造成的颌骨坏死临床表现较严重，且目前没有确切的根治方法，因此预防对于降低患病率和减轻患者负担至关重要。

2. BRONJ 定义

因使用 BPs 等药物而发生的以颌骨裸露、坏死为特征的并发症，命名为双膦酸盐相关性颌骨坏死(medication-related osteonecrosis of the jaws, BRONJ)指既往没有头颈部放射治疗史，过去或现在接受双膦酸盐治疗的患者出现超过 8 周仍未愈合的颌面部骨暴露[3]。

3. 流行病学

总体来说 BRONJ 发病率并不算高，口服 BPs 患者的发病率仅为 0.001%~0.05% [4]；基于治疗骨质疏松目的，接受 BPs 等抗骨吸收药物静脉输注的患者 BRONJ 发病率稍高(0.017%~0.35%) [5]；相比而言，因肿瘤治疗接受静脉 BPs 类药物治疗患者，BRONJ 发病率显著升高(2.8%~4.3%) [6]。牙拔除术是 BRONJ 的主要诱因，有 60%~70%的 BRONJ 患者在发病前接受了拔牙手术[7]。有报道[4] [7]证实，有 BRONJ 相关药物治疗病史的患者接受拔牙手术后，发病率为 5.9%。

4. 发病机制

目前公认的 BRONJ 的发病机制主要有：颌骨代谢失衡[8]、血管生成抑制[9] [10] [11]、局部微生物感染[12] [13]、免疫功能紊乱[10] [14]、软组织毒性[15] [16] [17]等。针对如上发病机制提出对双膦酸盐相关性颌骨坏死的预防措施。

5. 危险因素

包括：局部因素、全身因素、药物相关因素、风险患者的类别、生活习惯等，具体见表 1。

Table 1. Risk factors for BRONJ
表 1. BRONJ 发生的危险因素

局部因素[18]	全身因素	药物相关因素	风险患者的类别[19]	生活习惯[20]
口腔牙周感染、不合适的活动义齿、种植体周围炎症；拔牙、种植体手术、牙根治疗手术、骨再生手术	全身系统性疾病如糖尿病、类风湿性关节炎、低钙血症、甲状旁腺功能亢进、遗传因素和基础疾病如实体瘤、多发性骨髓瘤、骨质疏松症等	药物的类型、给药途径、累计剂量、治疗持续时间、支持性护理(如化疗、类固醇、沙利度胺)等	癌症患者或骨质疏松症患者	吸烟、饮酒、肥胖

6. 临床分期与治疗

目前尚无明确的治疗策略，主要根据临床分期制定治疗方法[21]，见表 2。

Table 2. System resulting data of standard experiment
表 2. 标准试验系统结果数据

临床分期	临床特点	治疗建议
危险期	无任何主观症状，无骨坏死表现	无需治疗，口腔卫生宣教
0 期	无骨坏死及骨暴露，有非特异的临床症状，可能发生进一步病变	全身系统治疗，包括止痛剂和抗生素的应用
I 期	有骨暴露和骨坏死，无临床症状，无感染征兆	抗菌含漱液，临床定期随访，对患者进行 BRONJ 疾病的相关说明
II 期	骨暴露或骨坏死，伴局灶性感染	抗菌含漱液，全身抗生素治疗控制疼痛，游离死骨表浅清创，及减轻软组织刺激
III 期	骨暴露或骨坏死，伴疼痛感染，同时具有以下一个或多个表现：病理性骨折，口外瘘道，病灶超出牙槽骨范围的颌骨	抗生素类含漱液含漱，全身抗生素治疗，控制疼痛，选择性局部清创或手术切除

7. 预防措施

由于目前尚无明确的治疗策略，所以采取必要的预防措施至关重要。BRONJ 预防意味着应用正确的方案治疗前和治疗中患者的一级预防；二级预防(即 BRONJ 的早期诊断) [19]。治疗前的一级预防包括消除或减少口腔的危险因素如残根残冠的处理、牙髓根尖周病的治疗、菌斑牙石的清除、活动性牙周病的控制、种植体周围炎症的治疗及无法保留的患牙的拔除。旨在恢复和/或维持良好的口腔健康，并降低病理状况或任何其他阴性事件发作的风险。因此牙科检查和口腔疾病的治疗至关重要。这就强调了口腔相关专业人员的重要性[22]。

7.1. 口腔相关专业人员应根据以下几点对服用 BPs 的患者发生 BRONJ 的几率进行评估

7.1.1. 需要进行的有创操作、患者的口腔健康状况

最近，牙周和种植体周围的感染已被强调为发生 BRONJ [23]的主要局部危险因素之一，且这些感染往往是治疗中或治疗后进行拔牙或种植术的主要原因。

7.1.2. 高危患者的类别

服用双膦酸盐类药物的主要是骨质疏松患者和癌症患者。研究表明，在接触 BPs 相关药物的癌症患者中，不良事件发生的频率在 0.2%至 6.7%之间，而骨质疏松等骨代谢疾病患者发生 BRONJ 的风险非常低，患病率在 0%至 0.4% [24]之间。然而，由于世界上受骨代谢疾病影响的患者数量巨大，就频率而言，约 40%受 BRONJ 影响的患者是非癌症患者[25]。

7.1.3. 全身健康状况，有无系统性疾病

研究发现，BRONJ 患者中有 58%(18/31)合并糖尿病(主要为 2 型糖尿病)或空腹血糖受损，显著高于接受 BPs 治疗但未患 BRONJ 者(12%) [26]，目前机制尚未研究清楚。一项回顾性研究[27]表明，BPs 联合糖皮质激素治疗的患者中，BRONJ 的发生率为(80/44784, 0.2%)，显著高于未服用激素组(260/191423, 0.1%, P = 0.013, OR = 1.3)，BPs 联合糖皮质激素治疗可增加 BRONJ 的发生风险。维生素 D 缺乏是否是 BRONJ 发生的危险因素上存在争议[28] [29] [30]。

7.1.4. 所服用的药物的种类

与伊班磷酸钠、帕米磷酸钠等 BPs 相比，唑来膦酸具有更强的骨吸收抑制作用，其发生 BRONJ 的相对风险增加了 5 倍[31]。目前癌症患者唑来膦酸使用方法为 4 mg，每 3~4 周输注 1 次，其 1 年、2 年、3 年 BRONJ 的发生率分别为 0.6%、0.9%、1.3% [21]，每给予 1 次剂量的 BPs，恶性肿瘤患者 BRONJ 的发生概率增加 1.0172 倍[32]。BPs 的种类、给药剂量及次数是 BRONJ 的独立危险因素。

7.2. 口腔相关专业人员对服用 BPs 前的患者的临床检查及操作

对于还未服用 BPs 类药物的患者在服用药物之前应进行常规的口腔检查、口腔卫生评估，消除口腔的危险因素，告知患者预防性口腔护理、保持口腔卫生、定期复查的重要性。

7.3. 口腔相关专业人员对服用 BPs 的患者在治疗过程中的预防措施

对于已在服用 BPs 类药物的患者，应根据治疗的口腔操作来评估风险水平，进而采取不同的预防措施。

7.3.1. 避免不必要的手术

患有骨代谢性疾病的患者在使用双膦酸盐期间，应尽可能避免进行口腔手术。如果必须进行手术则需要密切监测手术后的恢复情况，并根据需要进行治疗。

7.3.2. 对于风险水平较低的非侵入性口腔治疗

一般可常规进行，不需要应用特定的医疗和手术方案，但在操作中应更注意无菌原则。

7.3.3. 对于风险水平较高的侵入性和风险水平较高的口腔操作

如拔牙、牙周手术等最好是进行侵入性治疗与预防性抗生素治疗结合，青霉素、甲硝唑是常用的药物。最好逐个牙齿进行治疗，特别是在 Bps 相关药物尚未停用的情况下。为促进骨和软组织愈合，目前研究表明，如下措施会降低 BRONJ 的发生风险。

① 术前每天在家中使用 0.12%洗必泰消毒漱口水，从计划的牙科手术前 7 天开始，与抗生素治疗(如

肌肉注射氨苄西林/舒巴坦和口服甲硝唑)相结合，必须从干预前一天开始，并在干预后至少 6 天内使用。

② 在手术过程中，建议使用无肾上腺素的局麻，全厚度皮瓣，微创拔牙，拔牙后做牙槽成形术(如有必要)，应用无张力软组织缝合，以促进一期愈合。目前对于有创操作过程中预防 BRONJ 发生有如下研究进展：

浓缩生长因子：Daniel steller 等人[33]通过划痕、MTT 等体外实验，Michele Miranda 等人[33]通过回顾性研究证明富血小板血浆(platelet rich plasma, PRP)和富血小板纤维蛋白(Platelet-rich fibrin, PRF)可促进成骨细胞的沉降、粘附、增殖和迁移，从而改善创面愈合。由于浓缩生长因子降解较快，张圣敏等人[34]通过动物实验证明浓缩生长因子负载脂肪干细胞对于 BRONJ 的发生有预防作用，可能与浓缩生长因子具备三维聚合物的网络式纤维蛋白结构，可为脂肪干细胞诱导组织修复与再生提供可靠支架有关。

干细胞细胞外囊泡：f. Watanabe1 等人[35] [36]通过体外、体内实验表明干细胞细胞外囊泡(Stem cell extracellular vesicles, msc-ev)在干细胞、成骨细胞和成纤维细胞中可防止唑来膦酸诱导的衰老，并减少炎症细胞因子。此外，给药 msc-ev 可以防止参与伤口愈合的细胞衰老和衰老细胞周围慢性炎症的扩散，从而促进血管生成和骨再生，预防 BRONJ。

四面体骨架核酸(tetrahedral framework nucleic acid, tFNA)：Dan Zhao 等人[4] [37]采用了一种新的四面体框架核酸(tFNA)，它可以促进血管生成，拮抗 ZOL 对破骨细胞分化成熟的抑制作用，有效抑制 BRONJ 的形成。

骨形态发生蛋白 2：Gary I. Brierly [38]、Ji-Su OH [39]、Yukie Tanaka [40]等人通过骨形态发生蛋白 2 与 β-磷酸三钙、明胶海绵、水凝胶的联合应用证明可以使破骨细胞活性、骨体积、骨细胞密度增加，并减少与 BRONJ 相关的一些组织学特征。

光动力疗法：Farzin Sarkarat [41]通过初步动物实验证明光动力疗法具有抗菌和杀菌的特性或潜在的成骨细胞生物刺激作用。可在临床和组织病理学上减少或预防大鼠 BRONJ 的发生。

透明质酸：Farzin Sarkarat 等人[42]通过动物实验证明透明质酸，特别是透明质酸 + 可吸收明胶海绵似乎是预防或治疗 BRONJ 的合适方法。可能与透明质酸对骨生长和矿化有促进作用有关。

双向磷酸钙颗粒：Siri Paulo 等人[43]通过建立 BRONJ 体内模型。在核医学、放射学、宏观观察和组织学分析方面对动物进行评价，实验结果显示磷酸钙陶瓷能够限制唑来膦酸盐在体内的毒性，并促进愈合。

组抑素-1：Martín Castro 等人[44]通过唑来膦酸，组抑素-1 或其组合的影响在细胞毒性和细胞迁移测定中进行了评估。结果显示组抑素-1 在唑来膦酸激发后恢复了两种细胞系的细胞活力和迁移。因为组抑素-1 抵消了唑来膦酸的细胞毒性和抗迁移作用，并在体外恢复了血管生成能力。

药物假期：Sven Otto 等人[45]在动物模型中给予为期六周的药物假期，通过其结果认为围手术期药物假期预防 BRONJ 的效果明显。但还有学者认为 BPs 类药物半衰期长，药物假期的作用效果仍存在争议。

此外，尚有对白藜芦醇[46]、香叶酰香叶醇[47]、臭氧化油[48]、氟伐他汀[49]等对于 BRONJ 预防作用的研究。2020 年 Demircan 等[50]的病例对照研究评估了 MRONJ 患者的血清骨代谢标志物水平，结果发现：与健康对照者相比，MRONJ 患者的 VitD 水平较低，因此推测适当补充维生素 D 和钙等也可以降低 BRONJ 的发生率，提高患者的生活质量。对于优化药物治疗策略：合理用药、减少用药剂量和疗程、药物间歇使用、药物选择的个体化来降低发生药物性颌骨坏死的风险等问题尚在探索中。

8. BRONJ 的早期诊断

8.1. 详细病史

BRONJ 通常是在患者接受双膦酸治疗后出现的，因此医生需要询问患者是否正在或曾经接受过双膦

酸治疗。此外，患者的口腔卫生和牙齿状况等也是需要注意的因素。

8.2. 牙科检查

口腔医生可以通过检查患者的口腔和颌骨来判断 BRONJ 的早期症状。这些症状包括口腔疼痛、牙齿松动、颌骨肿胀和口腔溃疡等。

8.3. 影像学检查

口腔医生可以通过 X 线、CT 扫描和磁共振成像等影像学检查来判断 BRONJ 的早期症状。判断颌骨结构是否有异常现象。

8.4. 生物标志物检测

目前研究人员正在探索 BRONJ 的生物标志物，如血清中的骨代谢标志物、炎症标志物、组织标志物等，当它们的水平异常时可能暗示 BRONJ 的发生。但这些生物标志物目前仍处于研究阶段，只能作为一种诊断的辅助手段。

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