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· 综述 ·

## 局部用药在口腔黏膜疾病中的应用现状及展望

倪广成<sup>1</sup>, 但红霞<sup>1</sup>, 赵行<sup>2</sup>, 陈谦明<sup>1</sup>

1. 口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院黏膜科, 四川成都(610041); 2. 口腔疾病研究国家重点实验室 国家口腔疾病临床医学研究中心 四川大学华西口腔医院, 四川成都(610041)

**【摘要】** 口腔黏膜病是主要累及口腔黏膜及周围软组织的一类疾病总称。在口腔黏膜疾病治疗中,因解剖位置的特殊性,局部给药操作简便;药物易于在病损局部富集;同时还可以避免因全身用药而引起的不良反应。局部用药目前已成为口腔黏膜疾病治疗的重要甚至首选方案。临床常用的口腔黏膜局部用药种类多样,包括糖皮质激素如曲安奈德、免疫调节药物如他克莫司、消毒防腐药物如氯己定、止痛药物如利多卡因,中成药如芦荟凝胶等。这些局部药物中,以含漱液、喷雾剂等液体剂型应用最为广泛,这类制剂使用简便,但因口腔环境与功能的特殊性,并不利于药物局部停留。为解决这一问题,学者们对药物的剂型进行了不断改良,开发了一系列凝胶、软膏等半固体药物制剂,部分已在临床工作中发挥良好的疗效;此外,贴膜、贴片等固体药物制剂虽在口腔黏膜疾病临床治疗中鲜有应用,也已有大量基础研究被报道,并有望成为今后的主流剂型。总体而言,随着剂型的改良,局部给药在口腔黏膜疾病的治疗中发挥着越来越重要的作用。笔者将结合基础研究与临床报道,对局部用药在口腔黏膜疾病治疗中的应用现状进行综述。

**【关键词】** 口腔黏膜病; 局部给药; 药物剂型; 含漱液; 喷雾剂; 凝胶; 软膏; 曲安奈德; 他克莫司; 氯己定; 利多卡因; 芦荟凝胶

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**Application status and prospects of topical drug therapy in oral mucosal diseases** NI Guangcheng<sup>1</sup>, DAN Hongxia<sup>1</sup>, ZHAO Hang<sup>2</sup>, CHEN Qianming<sup>1</sup>. 1. State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & Department of Oral Mucosa, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China; 2. State Key Laboratory of Oral Diseases & National Clinical Research Center for Oral Diseases & West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China

Corresponding author: ZHAO Hang, Email: zhaohanghy@scu.edu.cn, Tel: 86-28-85501484

**【Abstract】** Oral mucosal disease is a general term for a type of disease that mainly affects the oral mucosa and surrounding soft tissues. In the treatment of oral mucosal diseases, due to the particularity of the anatomical location, the use of topical administration is relatively simple and convenient; drugs can easily accumulate in the lesions, and at the same time, they can also avoid adverse reactions caused by systemic drug delivery. Topical administration has become an important and even preferred option for the treatment of oral mucosal diseases. There are various types of topically used drugs for oral mucosal diseases, such as glucocorticoids (triamcinolone acetonide), immunomodulatory drugs (tacrolimus), antiseptic drugs (chlorhexidine), pain relievers (lidocaine) and proprietary Chinese medicines (aloe vera gel). Among these drugs, although the most widely used liquid formulations such as gargles and sprays are easy to use, they are not conducive to local retention of drugs due to the particularity of the oral environment and function. Based on this, researchers have continuously improved the dosage form of the drug, and developed a series of semi-solid pharmaceuti-

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**【作者简介】** 倪广成, 医师, 硕士, Email: ngchx@foxmail.com

**【通信作者】** 赵行, 教授, 博士, Email: zhaohanghy@scu.edu.cn, Tel: 86-28-85501484



微信公众号

cal preparations such as gels and ointments, some of which have exerted good curative effects in clinical work. In addition, although films, patches and other solid oral mucosal topical pharmaceutical preparations have few clinical applications, they have also been widely researched and described and are expected to become the mainstream dosage form in the future. In general, with the improvement of dosage forms, topical administration is playing an increasingly important role in the treatment of oral mucosal diseases. Therefore, combined with basic research and clinical reports, this article reviews the application of topical drug delivery in the treatment of oral mucosal diseases.

**【Key words】** oral mucosal disease; topical administration; drug dosage forms; gargles; sprays; gel; ointments; triamcinolone acetonide; tacrolimus; chlorhexidine; lidocaine; aloe vera gel

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口腔黏膜病是主要累及口腔黏膜及周围软组织的一类常见疾病的总称,其类型多样、种类众多且病因复杂<sup>[1]</sup>。已有研究指明,药物可以透过口腔黏膜进行局部甚至全身递送,从而发挥相应的药理学作用<sup>[2]</sup>。由于解剖位置的特殊性,口腔黏膜局部给药操作简便,药物易富集于病损,同时可以避免因全身用药而引起的不良反应,目前通常作为口腔黏膜疾病治疗中重要甚至首选的方案,大量临床及实验室相关研究也被报道。笔者对口腔黏膜疾病治疗中常用的局部药物制剂进行总结,以

期为后续口腔黏膜临床治疗与药物开发提供帮助。

## 1 液体制剂

如图1所示,包括含漱剂、喷雾剂及注射剂在内的多种液体制剂,在口腔扁平苔藓(oral lichen planus, OLP)、复发性阿弗他溃疡(recurrent aphthous ulcer, RAU)等口腔黏膜常见疾病中广泛应用,其使用方法简便,患者依从性良好。

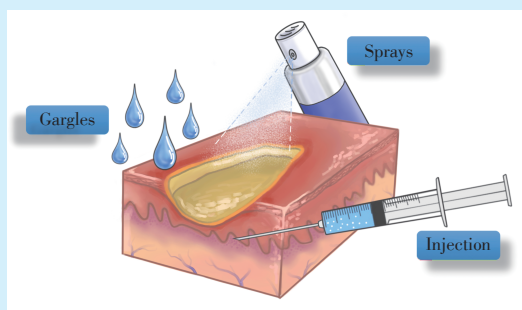


Figure 1 Application of liquid preparations in the topical treatment of oral mucosal diseases

图1 液体制剂在口腔黏膜疾病局部治疗的应用

### 1.1 含漱剂

含漱剂是在口腔黏膜疾病治疗中应用广泛的一类液体制剂,其种类多样,成分差异较大,但多数均旨在口腔黏膜病损局部发挥消毒防腐或促进组织修复的作用。例如,基于广谱抗菌药物葡萄糖酸氯己定的含漱剂,已被证实可用于预防化疗引起的口腔黏膜炎<sup>[3]</sup>,并且其对口腔黏膜创面的愈合也具有一定的促进作用<sup>[4]</sup>。而碱性的碳酸氢钠通过改变真菌生存所需酸性环境,广泛应用于真菌感染引起的口腔黏膜疾病,同时它在并发口腔黏膜炎的肿瘤患者中亦可以发挥良好的治疗效

果<sup>[5]</sup>。此外,一些基于硼砂、洋甘菊等中药的含漱剂<sup>[6]</sup>也在口腔黏膜疾病局部治疗中发挥重要作用。

### 1.2 喷雾剂

喷雾剂可将内容液体以雾状释放并分布于口腔黏膜病损区域。目前国内文献报道的此类剂型药物多为中成药制剂,譬如以蒲公英、忍冬藤等为有效成分的口腔炎喷雾剂,已被证实具有抗菌、抗炎、促进组织修复等功能,对包括疱疹性口炎<sup>[7]</sup>在内的多种口腔黏膜疾病具有辅助治疗作用。而国外相关文献则多为糖皮质激素类药物。例如, Kim等<sup>[8]</sup>开发了一种主要成分为曲安奈德的新型口腔

喷雾剂,可在黏膜界面形成薄膜并释放药物,被认为可用于口腔黏膜炎的治疗。此外,为规避首过消除等因素影响,一些全身应用的药物如大麻二酚也可以喷雾剂的形式,通过口腔黏膜实现全身药物递送<sup>[9]</sup>。

### 1.3 注射剂

口腔黏膜疾病局部治疗中应用的注射剂多为糖皮质激素相关制剂,多以局部封闭注射的方式给药,即通过在病损基底部注射以实现药物的局部富集,有效避免生理条件下口腔内唾液、食物、机械运动等因素对药物的冲刷,延长药物局部作用时间。在OLP局部治疗中,国内外已有大量文献肯定了局部注射曲安奈德、倍他米松等糖皮质激素<sup>[10]</sup>的治疗效果及安全性。而在口腔黏膜下纤

维性变(oral submucosal fibrosis, OSF)的治疗中,局部注射糖皮质激素也被证实可有效缓解疼痛症状,改善张口受限<sup>[11-12]</sup>。

## 2 半固体制剂

生理条件下,口腔承担着咀嚼、言语等生理功能,此过程中,唾液及外源性的食物、液体不断冲刷黏膜,使得液体制剂难以长时间留存于病损局部,降低了药物疗效。

基于此,研究者们开发了一系列半固体药物制剂,如软膏、凝胶、糊剂等,旨在延长药物在黏膜局部的作用时间,从而增强疗效。如图2所示,此类药物多通过局部涂抹的方式给药。

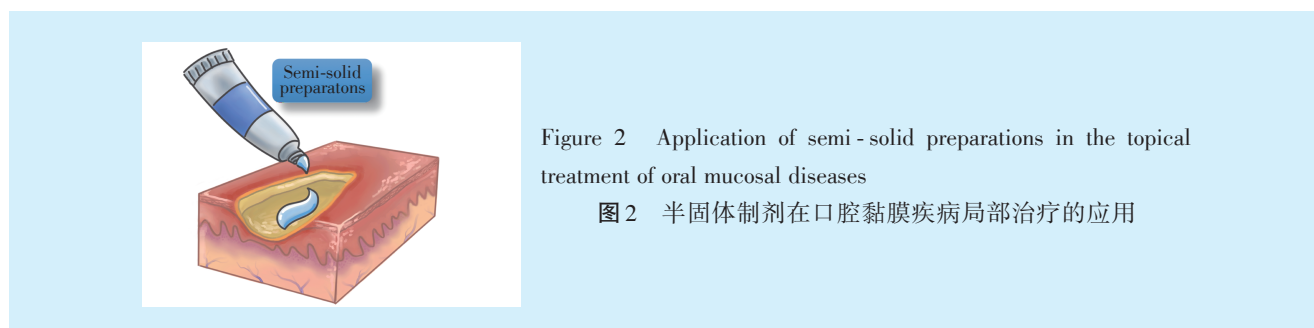


Figure 2 Application of semi-solid preparations in the topical treatment of oral mucosal diseases

图2 半固体制剂在口腔黏膜疾病局部治疗的应用

### 2.1 糖皮质激素类药物

由于强大的抗炎、抗免疫作用,糖皮质激素类药物在包括糜烂型OLP、RAU等口腔黏膜疾病局部治疗中作为一线用药,其中,曲安奈德相关制剂被广泛报道。例如,Siponen等<sup>[13]</sup>指出,0.1%曲安奈德糊剂对OLP具有良好的治疗效果;此外,亦有研究证实,0.1%曲安奈德口腔软膏在RAU的治疗中也具有良好的作用<sup>[14]</sup>。

而作为强效糖皮质激素,丙酸氯倍他索软膏原用于银屑病等皮肤病的局部治疗,但目前已证实其在某些口腔黏膜疾病中同样具有治疗作用。例如,Arduino等<sup>[15]</sup>在对32例伴疼痛症状的OLP患者进行随机对照试验后发现,局部应用0.05%丙酸氯倍他索软膏可明显缓解疼痛;亦有研究指出该制剂可用于RAU患者的治疗<sup>[16]</sup>。值得一提的是,尽管大量的临床试验基于0.05%浓度的氯倍他索,但已有研究证明,0.025%丙酸氯倍他索制剂同样可有效缓解患者症状与体征<sup>[17]</sup>。因此,临床工作中,或可使用较低浓度的氯倍他索制剂,以规避可能出现的不良反应。

此外,其他半固体制剂的糖皮质激素在口腔黏膜疾病的治疗中也存在零星报道,此处不一一枚举。需注意的是,长期局部应用糖皮质激素类药物,可能增加口腔念珠菌感染的风险,因此,在使用糖皮质激素治疗的同时,可联合应用碳酸氢钠或复方氯己定含漱液等抗真菌药物进行预防。

### 2.2 非激素类抗炎药物及免疫调节剂

某些非激素类的抗炎或免疫调节药物亦在口腔黏膜疾病治疗中做出一定贡献。例如,由日本开发的氨来咕诺已被证实具有良好的抗炎及免疫调节作用,在1996年被批准用于治疗RAU。其具体的作用机制被猜测可能与减少肥大细胞中组胺和白三烯的释放有关<sup>[18]</sup>。目前,氨来咕诺主要以5%糊剂的形式在全球范围内应用,对包括RAU在内的各类口腔溃疡具有较好疗效<sup>[14]</sup>。此外,亦有少数研究报道了该制剂在OLP治疗中的作用<sup>[19]</sup>。

而在1984年,日本学者从链霉素中提取出了具有强大免疫抑制作用的他克莫司,依赖于对钙调神经磷酸酶活性的特异性抑制,此药物可调控免疫应答因子白细胞介素2的激活<sup>[20]</sup>。基于此,他

克莫司起初被批准用于预防器官移植患者术后排斥反应,但很快研究者们就发现其在OLP的治疗中显示出不弱于氯倍他索等糖皮质激素的疗效<sup>[21]</sup>,也有研究报道了他克莫司软膏在唇炎<sup>[22]</sup>、盘状红斑狼疮<sup>[23]</sup>等口腔黏膜疾病中的应用。

### 2.3 局麻止痛药物

口腔黏膜疾病可表现出明显的疼痛不适,因此,必要情况下可指导患者局部应用止痛药物,例如局部麻醉药物利多卡因。通过作用于伤害感受器的电压门控钠离子通道,利多卡因可阻止疼痛感觉冲动传递至大脑<sup>[24]</sup>。Hindocha等<sup>[25]</sup>通过随机交叉试验指出,5%利多卡因凝胶局部应用于口腔黏膜后,可迅速有效减轻因针刺等造成的疼痛症状。类似的,Nair等<sup>[26]</sup>在另一项随机对照试验中发现,同样作为局麻药物,20%苯佐卡因凝胶,表现出较利多卡因凝胶更好的口腔黏膜麻醉镇痛效果。

### 2.4 促组织修复药物

在口腔黏膜疾病治疗中,有时还可局部给予促进组织修复的药物,例如重组人表皮生长因子(recombinant human epidermal growth factor, rhEGF)。表皮生长因子(epidermal growth factor, EGF)是由53个氨基酸残基组成的短肽,可通过自分泌和旁分泌的方式作用于相应的受体,在加快上皮细胞的增殖、迁移及分化的同时,也可以促进新生血管和肉芽组织的形成,促进创面愈合<sup>[27]</sup>。通过基因重组技术制备的rhEGF在结构和功能上与EGF高度一致,其凝胶制剂对化疗引起的口腔黏膜炎<sup>[28]</sup>等口腔黏膜疾病具有一定的治疗作用。此外,重组牛碱性成纤维细胞生长因子(recombinant bovine

basic fibroblast growth factor, rb-bFGF)也已被证实可有效促进血管、细胞的增殖以及细胞分化等,有助于创面的愈合<sup>[29]</sup>。亦有报道将其应用于儿童OLP<sup>[30]</sup>等疾病的治疗。需要注意的是,以上两种药物在生理条件下易被黏膜中的蛋白酶降解,丧失生物活性,因此,同样有研究旨在提高此类药物的稳定性<sup>[31]</sup>。

### 2.5 中成药

一些中成药的半固体制剂也在口腔黏膜疾病的局部治疗中有着不俗表现,其中芦荟凝胶应用较为广泛。因含有蒽醌类、维生素、糖类、脂类等活性物质,芦荟具有广泛的药理作用,包括抗炎、抗病毒、免疫调节等。Ali等<sup>[32]</sup>通过系统评价,对芦荟治疗OLP的安全性及有效性给予充分的肯定;Shi等<sup>[33]</sup>研究发现,在35例RAU患者中,芦荟凝胶表现出良好的治疗效果。此外,在包括OSF<sup>[34]</sup>、化疗性口炎<sup>[35]</sup>等口腔黏膜疾病的治疗中,均存在芦荟半固体制剂应用的报道。

## 3 固体制剂

在半固体制剂基础上,研究者们近些年尝试开发口腔黏膜局部用药固体制剂,例如口腔贴膜。如图3所示,此类制剂将药物溶解或分散于壳聚糖等具有成膜性质的材料中,并辅以粘附层(协助贴膜的固定)、隔湿层(防止唾液的溶解冲刷)等,实现药物的局部缓释,从而延长药物作用时间。目前,相关研究多停留在实验室阶段,仅少数制剂应用于临床治疗。

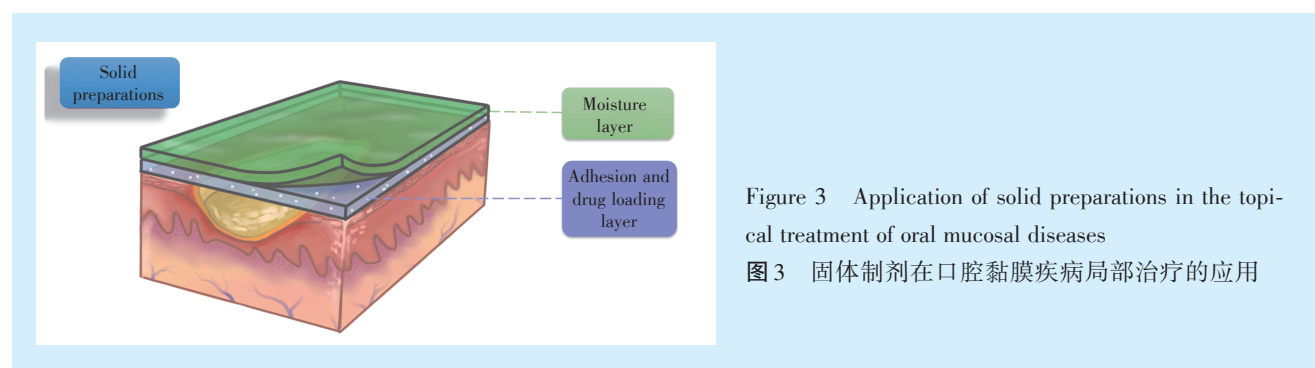


Figure 3 Application of solid preparations in the topical treatment of oral mucosal diseases

图3 固体制剂在口腔黏膜疾病局部治疗的应用

目前应用于口腔黏膜疾病临床局部治疗的固体制剂相对少见,例如,Pakravan等<sup>[36]</sup>报道了一种基于曲安奈德的口腔贴膜,证实其对放射性口炎具有良好的治疗效果。有趣的是,还有为数不少

的口腔贴膜并非用于口腔黏膜疾病,而是借助口腔黏膜进行全身药物递送,用于治疗神经或精神系统等疾患。例如,基于经典的镇痛药物芬太尼构建的颊黏膜贴膜具有良好的镇痛作用,可通过

颊黏膜吸收药物,有效避免了肝脏首过代谢所致药物失活,已被证实对癌性疼痛具有良好的镇痛作用<sup>[37]</sup>。

而在相关固体制剂的开发中,亦有大量研究尚停留于实验室阶段。例如,Ryu等<sup>[38]</sup>通过引入邻苯二酚结构对壳聚糖进行改性,冻干处理并搭载曲安奈德,这种新型材料 Chitoral 在兔口腔溃疡模型中表现出良好的疗效;Colley等<sup>[39]</sup>则通过电纺丝技术,构建了粘附层与隔湿层结合的双层膜,在保持良好粘附性的同时,还实现了在猪颊黏膜定点缓释氯倍他索,具有口腔黏膜应用潜能。此类研

究在近些年被广泛报道,也被越来越多的研究者所关注,相信这会为之后的口腔黏膜贴剂的开发与应用提供坚实的理论基础。

#### 4 总结与展望

笔者对口腔黏膜局部治疗的代表性药物总结如表1所示,目前它们在口腔黏膜疾病的治疗中发挥着重要的作用,其剂型也得到不断改良以更加适用于口腔黏膜环境。同时,值得注意的是,虽然大多数研究均旨在通过改良剂型来提高药物作用,但同样可以在给药方式上寻求突破,譬如本文

表1 口腔黏膜疾病局部治疗常用药物信息

Table 1 Information on commonly used drugs for topical treatment of oral mucosal diseases

Drug	Main ingredient	Application	Usage	Mechanism
<b>Solution preparation</b>				
Compound chlorhexidine gargle	Chlorhexidine gluconate, metronidazole	Treatment of pericoronitis, oral ulcers and erosions	Gargle	Broad spectrum antibacterial and antifungal
Sodium bicarbonate	Sodium bicarbonate	Prevention and treatment of oral fungal infections	2%-4% w/v, gargle	Antifungal by adjusting pH
Compound borax gargle	Borax, phenol, glycerin, et al	Treatment of oral ulcers, erosions and stomatitis	Gargle	Disinfection, bacteriostatic effect and protect oral mucosa
Stomatitis spray	Honeycomb, dandelion, honeysuckle vine, et al	Treatment of stomatitis, pharyngitis, and oral ulcers	Spray	Anti-inflammatory, antibacterial and tissue repair
Compound betamethasone injection	Betamethasone	Treatment of oral ulcers and erosions	Injection	Powerful anti-inflammatory and immunosuppressive
Triamcinolone acetonide injection	Triamcinolone acetonide	Treatment of oral ulcers and erosions	Injection	Powerful anti-inflammatory and immunosuppressive
<b>Semi-solid preparation</b>				
Triamcinolone acetonide oral ointment	Triamcinolone acetonide	Treatment of oral ulcers and erosions	0.1% w/w, smear	Powerful anti-inflammatory and immunosuppressive
Clobetasol propionate cream	Clobetasol propionate	Treatment of oral ulcers and erosions	0.05% w/w, smear	Powerful anti-inflammatory and immunosuppressive
Amlexanox oral paste	Amlexanox	Treatment of oral ulcers and erosions	5% w/w, smear	Inhibit the formation and release of inflammatory factors
Tacrolimus ointment	Tacrolimus	Treatment of OLP, cheilitis, et al.	0.03%/0.1% w/w, smear	Inhibits the activation of interleukin-2
Lidocaine gel	Lidocaine	Relieve pain in the oral mucosa	5% w/w, smear	Blocks the transmission of pain sensation urges
rhEGFgel	rhEGF	Healing of wounds like ulcers	Smear	Promote cell growth and capillary regeneration
rb-bFGF Gel	rb-bFGF	Healing of wounds like ulcers	Smear	Promote cell growth and capillary regeneration
Aloe vera gel	Aloe-emodin, aloe anthrone, vitamins, et al.	Treatment of oral ulcers, erosions and stomatitis	Smear	Anti-inflammatory, antiviral, immunomodulatory, et al.
<b>Solid preparations</b>				
Triamcinolone acetonide oral patch	Triamcinolone acetonide	Treatment of oral ulcers and erosions	Paste on the oral mucosa	Powerful anti-inflammatory and immunosuppressive

EGF: epidermal growth factor; FGF: fibroblast growth factor; OLP: oral lichen planus

提及的局部封闭注射或在器械辅助下进行给药。此外,基于目前被广泛研究的可注射水凝胶<sup>[40]</sup>,今后可以结合药物剂型与给药方式的改良,双管齐下,进一步延长药物在目标病损组织的作用时间,提高疗效。期待并相信口腔黏膜疾病在未来会出现更好的局部药物治疗理念与方法。

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