

## 芦荟凝胶治疗巴马小型猪糖尿病慢性皮肤溃疡的实验研究\*

梁渝捷<sup>1</sup>, 李 艳<sup>1</sup>, 高芸艺<sup>1</sup>, 王 莉<sup>2</sup>, 冉兴无<sup>1△</sup>

1. 四川大学华西医院 内分泌代谢科 糖尿病足诊治中心 创面修复创新中心(成都 610041);

2. 成都华西海圻医药科技有限公司(国家成都新药安全性评价中心)(成都 610041)

**【摘要】目的** 研究局部应用芦荟凝胶(AVG)治疗巴马小型猪糖尿病慢性皮肤溃疡的有效性、安全性及其作用机制。**方法** 将糖尿病慢性皮肤溃疡模型猪随机分为芦荟凝胶每日给药(AVG QD)组、芦荟凝胶隔日给药(AVG QOD)组及糖尿病对照(DC)组;非糖尿病慢性皮肤溃疡模型猪设为非糖尿病对照(NDC)组。疗效评价指标包括创面完全愈合时间、肉芽生长率、愈合率以及皮肤病理组织学观察;以是否观察到不良反应评价安全性;同时检测创面肉芽组织miR21、miR29a、miR126、miR146a、miR155和miR210相对表达量的动态变化。**结果** ①疗效评估: NDC组完全愈合时间比DC组、AVG QD组及AVG QOD组短( $P < 0.05$ ), AVG QD组和AVG QOD组完全愈合时间较DC组短( $P < 0.05$ ), AVG QOD组完全愈合时间较AVG QD组短( $P < 0.05$ ), 芦荟凝胶治疗全过程未监测到不良反应发生。NDC组肉芽生长率高于DC组、AVG QD组及AVG QOD组( $P < 0.05$ )。NDC组创面愈合率高于DC组、AVG QD组及AVG QOD组( $P < 0.05$ ); AVG QOD组创面愈合率高于DC组与AVG QD组( $P < 0.05$ )。②组织病理学: HE染色光镜结果示AVG治疗后,创面愈合初期胶原纤维生成增多,真皮间质见微血管形成伴少许炎细胞浸润;完全愈合至一年后,表皮角化完全,胶原排列整齐有序,间质内见较多微血管分布。苦味酸天狼猩红特染结果示创面愈合初期以I型胶原增多为主,至创面完全愈合时III型胶原逐渐增多,整个过程胶原排列整齐有序。③microRNAs相对表达量: NDC组、AVG QD组及AVG QOD组miR21、miR126及miR210相对表达量均高于DC组( $P < 0.05$ ), miR29a、miR155相对表达量低于DC组( $P < 0.05$ ); NDC组miR146a相对表达量高于DC组( $P < 0.05$ )。**结论** 芦荟凝胶局部治疗可以缩短巴马小型猪糖尿病慢性创面完全愈合时间,且隔日治疗组完全愈合时间快于每日治疗组,治疗过程中未发现不良反应发生,机制可能与其上调创面肉芽组织miR21、miR126及miR210表达,降低miR29a和miR155表达有关。

**【关键词】** 芦荟凝胶 巴马小型猪 糖尿病 慢性皮肤溃疡 microRNAs 创面愈合

### Experimental Study of Using Aloe Vera Gel to Treat Diabetic Chronic Cutaneous Ulcers in Bama Miniature Pigs

LIANG Yu-jie<sup>1</sup>, LI Yan<sup>1</sup>, GAO Yun-yi<sup>1</sup>, WANG Li<sup>2</sup>, RAN Xing-wu<sup>1△</sup>. 1. Innovation Center for Wound Repair, Diabetic Foot Care Center, Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu 610041, China; 2. West China-Frontier PharmaTech Co. Ltd. (National Chengdu Center for Safety Evaluation of New Drugs), Chengdu 610041, China

△ Corresponding author, E-mail: ranxingwu@163.com

**【Abstract】 Objective** To investigate the efficacy, safety, and mechanism of topical application of aloe vera gel (AVG) to treat diabetic chronic cutaneous ulcers in Bama miniature pigs. **Methods** The Bama miniature pig model of diabetic chronic skin wounds was constructed and the model pigs were randomly assigned to AVG daily administration group (AVG QD), aloe vera gel every-other-day administration group (AVG QOD), and diabetic control group (DC). A non-diabetic chronic skin wounds model pig was set as the non-diabetic control group (NDC). Treatment efficacy was evaluated based on the amount of time needed for complete healing of the wounds, healing rates, granulation growth rates, and skin histopathological changes. Safety was evaluated according to whether adverse reactions were observed. In addition, the dynamic changes of the relative expression levels of miR21, miR29a, miR126, miR146a, miR155, and miR210 in wound granulation tissues were examined. **Results** 1) Efficacy and safety: The amount of time needed for complete healing of the wounds was shorter in the NDC group than those of the three other groups, DC group, AVG QD group, and AVG QOD group (all  $P < 0.05$ ). The amount of time needed for complete healing of the wounds was shorter in the AVG QD group and AVG QOD group than that of DC group (all  $P < 0.05$ ). The amount of time needed for complete healing of the wounds was shorter in the AVG QOD group than that of AVG QD group (all  $P < 0.05$ ). No adverse reactions

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△ 通信作者, E-mail: ranxingwu@163.com

were detected in the whole process of AVG topical treatment. The granulation growth rate of NDC group was higher than those of DC group, AVG QD group, and AVG QOD group (all  $P<0.05$ ). The wound healing rate of NDC group was higher than those of DC group, AVG QD group, and AVG QOD group (all  $P<0.05$ ); the wound healing rate of AVG QOD group was higher than those of DC group and AVG QD group (all  $P<0.05$ ). 2) Histopathology: The results of HE staining light microscopy showed that collagen fiber production increased, and that microvascular formation with slight inflammatory cell infiltration was observed in the dermal interstitium at the initial stage of wound healing after AVG treatment. One year of after complete healing, pathological examination results of wound healing skin showed that the epidermal keratinization was complete, that collagen was arranged neatly and orderly, and that many microvessels were found in the interstitium. The results of picric acid celestite scarlet staining showed that, after AVG treatment, type I collagen mainly increased in the initial stage of wound healing, type III collagen gradually increased when the wound healed completely, and the collagen was arranged neatly during the whole process. 3) The relative expression of microRNAs: The relative expression of miR21, miR126, and miR210 in NDC group, AVG QD group, and AVG QOD group were higher than that in DC group (all  $P<0.05$ ). The relative expression of miR29a and miR155 in NDC group, AVG QD group, and AVG QOD group was lower than that in DC group (all  $P<0.05$ ). The relative expression of miR146a in NDC group was higher than that in DC group ( $P<0.05$ ). **Conclusion** AVG topical application can shorten the time needed for complete healing of diabetic chronic wounds in Bama minipigs. The wound healing speed of the alternate-day treatment group was faster than that of the daily treatment group. No adverse reactions were observed over the course of the treatment. The mechanism may be related to the up-regulation of the expressions of miR21, miR126, and miR210 and the down-regulation of miR29a and miR155 in wound granulation tissue.

**【Key words】** Aloe vera gel    Bama minipigs    Diabetes mellitus    Chronic cutaneous ulcer  
microRNAs    Wound healing

慢性创面多见于糖尿病、创伤、长期卧床及下肢动静脉疾病等患者,经久不愈,严重影响患者生活质量。与欧美发达国家相似,糖尿病(32.6%)已成为我国慢性创面的主要致病原因之一<sup>[1]</sup>;在糖尿病所致的慢性创面中,又以糖尿病足溃疡(diabetic foot ulcer, DFU)占主导地位<sup>[2]</sup>。

近年来,虽然负压吸引闭式引流、自体/异体干细胞移植、重组人表皮生长因子、鼠神经成纤维细胞生长因子、自体富血小板凝胶等先进的治疗手段不断涌现,为DFU的治疗带来了革新性的变化,但由于DFU治疗时间长、治疗费用高及治愈率较低,临床上仍亟需探寻安全、有效、价格合理的治疗方法。

芦荟是芦荟属百合科肉质植物,品种繁多,含有多糖、蒽醌、糖蛋白、维生素和矿物质等多种药理活性物质<sup>[3]</sup>。其中芦荟多糖(aloe polysaccharide, APS)是其主要活性成分,富集芦荟多糖的敷料在缩小创面、减少增生性瘢痕、调节细胞因子和抗菌作用方面均优于传统敷料<sup>[4]</sup>。研究表明芦荟凝胶(aloe vera gel, AVG)具有预防压疮,促进烧烫伤、辐射伤、手术切口、皮肤移植供体部位及糖尿病足溃疡等各类急、慢性创面愈合的作用<sup>[5-9]</sup>,动物实验显示其安全性良好<sup>[10-12]</sup>,但芦荟促进创面愈合的可能机制并未完全阐明<sup>[13-16]</sup>。

微小RNA(microRNA, miRNA/miR)是重要的基因表达调控因子,通过抑制靶基因转录、翻译或降解mRNA,影响蛋白质合成与功能表达。miRNAs在创面愈合各个

阶段均发挥重要作用<sup>[17-18]</sup>。我们的前期研究发现,糖尿病慢性创面miR21、miR126、miR146a以及miR210低表达,miR29a和miR155高表达,可能是其难以愈合的原因<sup>[19]</sup>。因此,本研究目的在于探讨局部应用芦荟凝胶治疗巴马小型猪糖尿病慢性皮肤创面的有效性、安全性及其促进创面愈合的相关机制。

## 1 材料与方法

### 1.1 实验分组及给药方案

巴马小型猪糖尿病及慢性皮肤创面模型的构建方法参照李艳<sup>[19]</sup>的研究方法。共选取33月龄的巴马小型猪4只,其中3只为糖尿病慢性创面模型猪,随机分为糖尿病对照组(DC组)、芦荟凝胶每日一次换药组(AVG QD组)、芦荟凝胶隔日一次换药组(AVG QOD组);另1只为非糖尿病慢性创面模型猪,即非糖尿病对照组(NDC组)。麻醉下手术切除造创,脊柱旁开3 cm处,每间隔3~4 cm造1个3 cm×3 cm的创面。根据小型猪体长,NDC组造创面14个,DC组、AVG QD组各造创面18个、AVG QOD组造创面9个(图1)。NDC组、DC组每3日进行常规敷料更换,AVG QD组、AVG QOD组在此基础上,每日、隔日涂抹芦荟凝胶。实验动物饲养条件、室温、光照、分笼笼具面积、笼具定期消毒、喂养量占体质量的百分比、进水量等无差别。本研究已得到四川大学华西医院动物伦理委员会的批准(No. IACUC 2020214 A)。

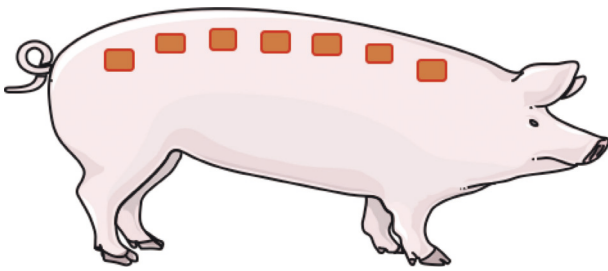


图1 小猪单侧背部创面模型图

Fig 1 Illustration of the model of diabetic chronic wounds on the back of a minipig on one side

## 1.2 实验药物和主要试剂

实验药物: 芦荟凝胶由成都华西海圻医药科技有限公司提供, 主要成分: 库拉索芦荟冻干粉、甘油、丙二醇、植物抗氧化剂等。

主要试剂: Bulge-Loop™ miRNA RT-qPCR Primer、RT-qPCR Starter Kit(广州锐博生物科技有限公司), RNAiso for Small RNA(Takara), DNase/RNase-free water for PCR(Bio-Rad); 苦味酸(台山市化工厂有限公司), 天狼猩红溶液(合肥博美生物科技有限公司)。

## 1.3 疗效评估

**1.3.1 疗效评价指标** 完全愈合时间: 创面被上皮完全覆盖所需要的时间; 治疗前测得创面初始体积(将生理盐水充满创面, 使用生理盐水的体积即为创面体积)和面积, 治疗后每3天测量一次; 计算D3、D6、D9及D12等4个时间点的肉芽组织生长率, 肉芽生长率=(创面初始体积-目前创面体积)/创面初始体积×100%; 愈合率=(创面初始面积-未愈合面积)/创面初始面积×100%, 面积测量采用“无菌薄膜勾边法+ImageJ”的方法计算<sup>[20]</sup>。

**1.3.2 皮肤组织学检查指标** 因为瘢痕组织重塑成熟至少需要1年, 为避免频繁取材对创面愈合产生不良影响, 我们在治疗后第15天(D15)、第60天(D60)以及完全愈合一年后(Y1)分三次对皮肤组织标本进行取材。但DC组小型猪在创面完全愈合后1月突发呕吐、便血、低体温等症状后死亡, 因此本组无Y1皮肤标本。通过HE染色观察皮肤及附属器结构、血管以及胶原排列情况, 苦味酸天狼猩红染色观察I、III型胶原变化。

## 1.4 肉芽组织取材和miRNAs检测

从开始治疗当天(D0)至第15天, 每3天取1次创面肉芽组织, 即D0, D3, D6, D9, D12及D15取材。具体过程如下: 创面消毒准备, 予以5%盐酸氯胺酮注射液(5 mg/kg)麻醉, 活检器取大小约1 cm<sup>3</sup>的肉芽组织, 液氮转运至-80℃冰箱保存。miRNAs检测严格按照说明书进行, NDC组miRNAs的动态变化仅作为DC组的对照, DC组miRNAs的动态变化作为实验组的对照, 以各组D0创面

为对照, 计算 $2^{-\Delta\Delta Ct}$ 作为治疗后各miRNA的相对表达量<sup>[21]</sup>。

## 1.5 统计学方法

计量资料用 $\bar{x} \pm s$ 表示, 计数资料以百分比表示。不同组别均数比较使用单因素方差分析, 组间多个时间点的数据分析使用两因素重复测量方差分析, 不符合球形检验者, 采用Greenhouse-Geisser(G-G)法校正, 组间有差异, 两两比较用Student-Newman-Keuls(SNK)检验,  $P \leq 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 疗效与副作用观察

NDC组创面完全愈合时间[(35.57±2.59) d]比DC组[(53.50±6.20) d]、AVG QD组[(47.83±4.42) d]及AVG QOD组[(43.00±2.60) d]短, 差异均有统计学意义( $P < 0.05$ ), AVG QD组、AVG QOD组愈合时间均比DC组短( $P < 0.05$ ), AVG QOD组愈合时间比AVG QD组短( $P < 0.05$ )。与非糖尿病慢性创面相比, 糖尿病慢性创面更难愈合; 与糖尿病常规治疗相比, 芦荟凝胶能缩短创面完全愈合时间, 且芦荟凝胶隔日给药完全愈合时间最短。

对照组和芦荟凝胶组各组创面愈合趋势较为一致(图2), NDC组和DC组创面干燥, AVG组创面湿润。NDC组、AVG QD组和AVG QOD组创面肉芽组织较新鲜, 上皮爬行较快, 痂皮易脱落, 较早出现完全愈合的创面, 而DC组创面内较多黄白色分泌物, 上皮爬行较慢, 痂皮紧贴不易脱落。NDC组整体瘢痕印迹明显, 与周围皮肤分界清, 瘢痕处无明显毛发生长, 触之质地较硬。AVG QD组和AVG QOD组整体瘢痕印迹差异不明显, 无明显毛发生长, 皮肤光滑, 触之质软。

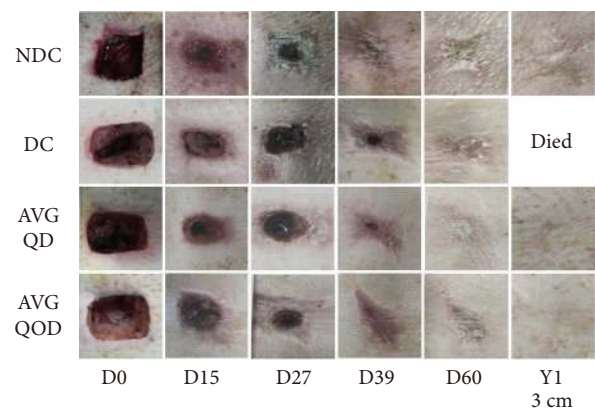


图2 创面愈合过程和皮肤瘢痕动态变化

Fig 2 Wound healing process and dynamic changes of skin scars

### 2.2 肉芽生长率和创面愈合率

两因素重复测量方差分析示, 肉芽生长率随时间而增加; 组别不同, 肉芽生长率不同, NDC组肉芽生长率

(93.7%±1.0%)分别高于DC组(86.6%±0.9%)、AVG QD组(80.6%±0.9%)以及AVG QOD组(83.8%±1.3%),差异均有统计学意义( $P < 0.05$ ), DC组肉芽生长率与AVG QOD组差异无统计学意义( $P > 0.05$ ),但两组肉芽生长率均高于AVG QD组,差异均有统计学意义( $P < 0.05$ )。AVG治疗并未能显著提高肉芽生长率。

相似地,创面愈合率随着时间变化而增加;组别不同,愈合率不同, NDC组愈合率(75.3%±0.8%)分别高于DC组(66.6%±0.7%)、AVG QD组(66.0%±0.7%)及AVG QOD组(72.7%±0.9%),差异均有统计学意义( $P < 0.05$ );AVG QOD组愈合率高于DC组及AVG QD组,差异均有统计学意义( $P < 0.05$ )。AVG QOD治疗能提升创面愈合率。

### 2.3 病理组织学观察

对治疗后D15、D60以及Y1的皮肤组织标本进行取材, HE染色(图3)结构分别显示:芦荟凝胶治疗炎症细胞浸润少,愈合过程胶原较致密,排列更整齐有序;DC组可见微血管明显扩张伴较多炎症细胞浸润,胶原排列紊乱且部分胶原变性;NDC组和AVG QD组真皮间质丰富的微血管和神经纤维丛,均可见数个毛囊。

苦味酸天狼猩红染色(图4)显示: D15时,以 I 型胶

原(橙红色)为主导,与NDC组、DC组相比,AVG QD组 I 型胶原显著增加; D60时,以 III 型胶原(绿色)为主,与NDC组、DC组相比,AVG QD组胶原排列更整齐有序; Y1时, NDC组、AVG QD组真皮层见 I 型胶原广泛分布,伴细网状绿色 III 型胶原。采用Image-Pro Plus图像分析系统计算NDC组、DC组、AVG QD组 I / III 型胶原纤维百分比,结果发现在创面修复早期 I / III 型胶原比值分别为 40.18、5.31、58.14, D60时为 1.47、0.14、0.74; Y1时NDC组与AVG QD组 I / III 型胶原比值为 6.19、5.93。

### 2.4 创面肉芽组织microRNAs表达的动态变化

两因素重复测量方差分析结果示各组间miRNAs整体表达量差异均有统计学意义( $P < 0.05$ ), NDC组(1.87±0.20)、AVG QD组(2.25±0.23)、AVG QOD组(1.86±0.23)miR21相对表达量都高于DC组(1.03±0.18),差异均有统计学意义( $P < 0.05$ )。NDC组(0.91±0.05)、AVG QD组(0.82±0.08)、AVG QOD组(0.85±0.06)miR29a相对表达量均低于DC组(1.30±0.05),差异均有统计学意义( $P < 0.05$ )。NDC组(1.65±0.24)、AVG QD组(1.50±0.14)、AVG QOD组(1.48±0.24)miR126相对表达量均高于DC组(0.75±0.17),差异均有统计学意义( $P < 0.05$ )。

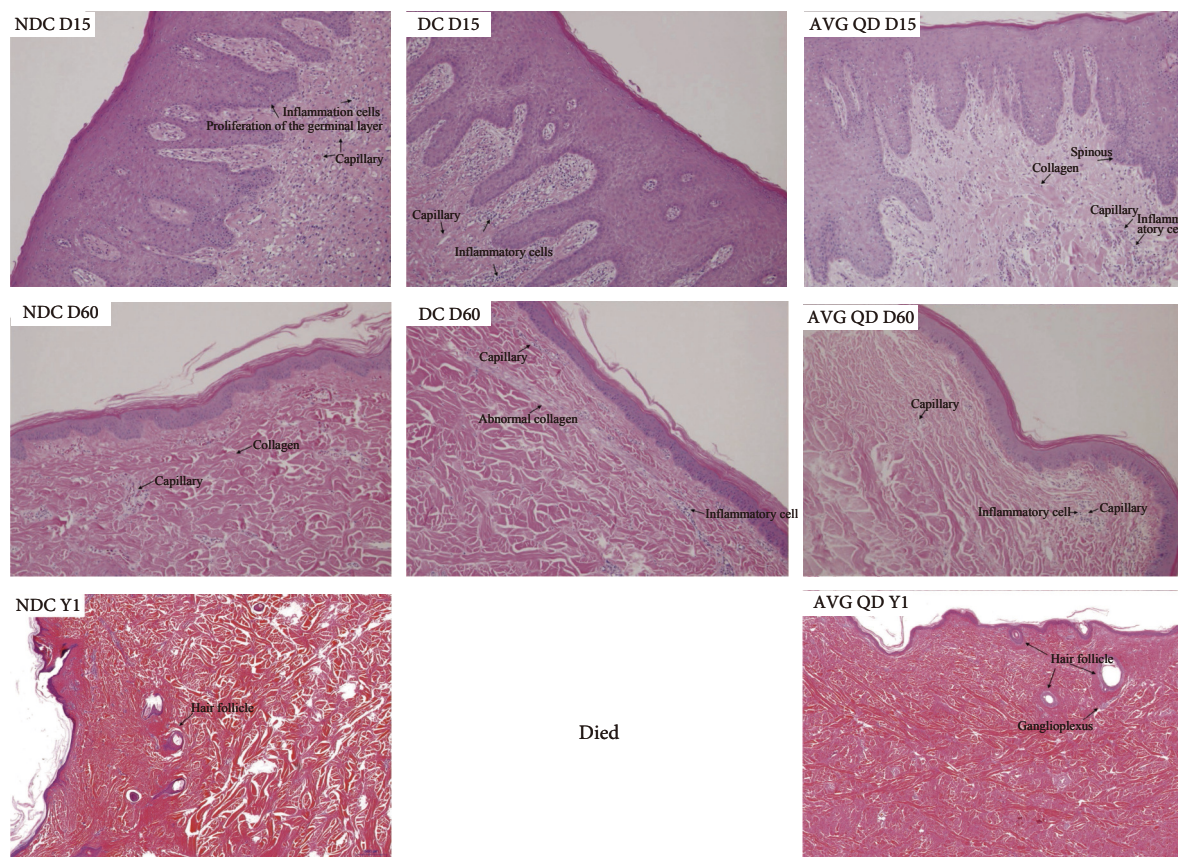


图 3 治疗后不同时间皮肤创面组织HE染色 (D15、D60:×10; Y1:×20)

Fig 3 HE staining of skin wound tissues after different periods of time post treatment (D15 and D60: ×10; Y1: ×20)

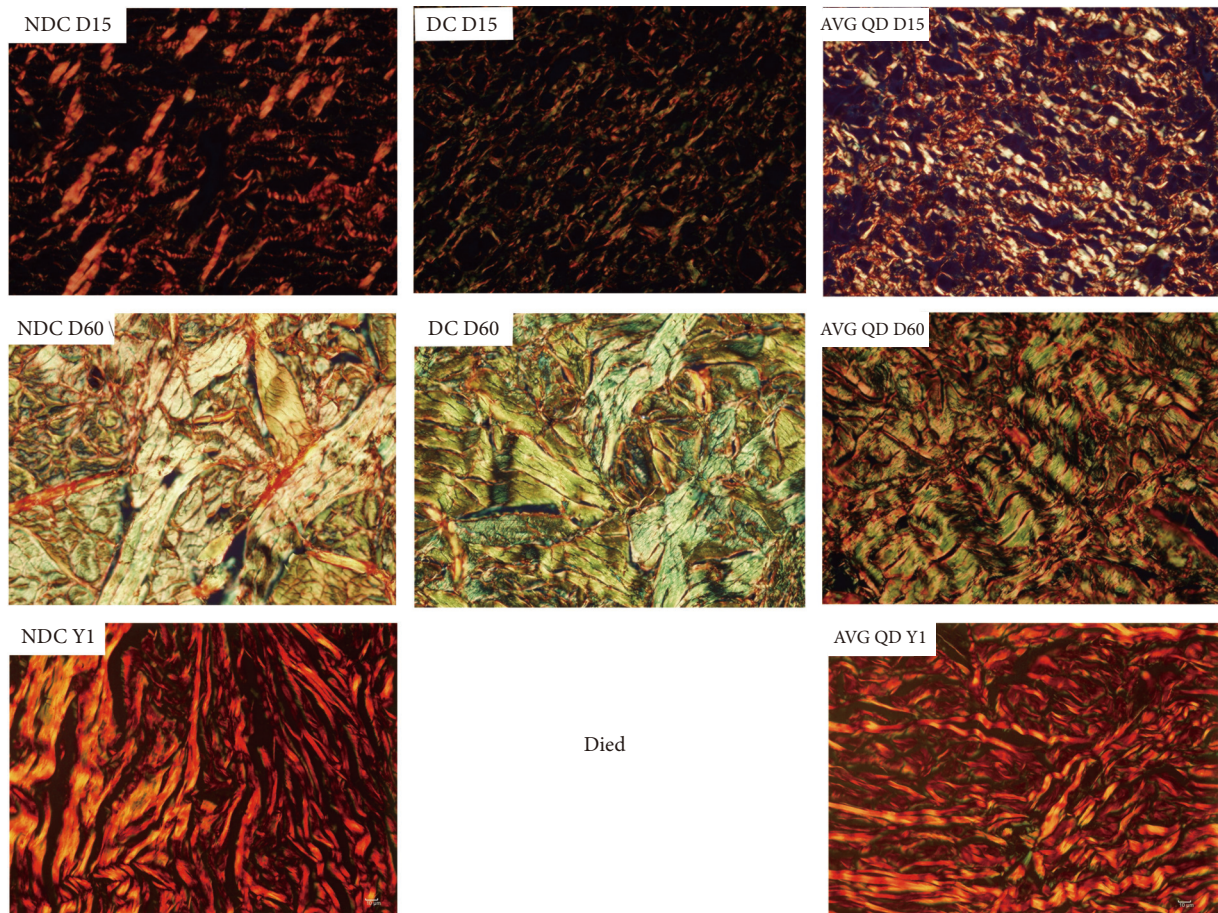


图4 治疗后不同时间皮肤创面组织天狼猩红染色( $\times 400$ )

Fig 4 Sirius Red staining of skin wound tissues after different periods of time post treatment ( $\times 400$ )

0.05)。NDC组( $1.85 \pm 0.17$ )miR146a相对表达量高于DC组( $1.15 \pm 0.12$ ), 差异有统计学意义( $P < 0.05$ ), DC组miR146a相对表达量与AVG QD组( $1.30 \pm 1.17$ )、AVG QOD组( $1.44 \pm 0.17$ )差异无统计学意义。DC组( $1.04 \pm 0.08$ )miR155相对表达量高于NDC组( $0.68 \pm 0.08$ )、AVG QD组( $0.78 \pm 0.06$ )、AVG QOD组( $0.82 \pm 0.07$ ), 差异均有统计学意义( $P$ 均 $< 0.05$ )。DC组( $1.06 \pm 0.11$ )miR210相对表达量低于NDC组( $1.54 \pm 0.14$ )、AVG QD组( $1.64 \pm 0.11$ )、AVG QOD组( $1.47 \pm 0.14$ ), 差异均有统计学意义( $P$ 均 $< 0.05$ )。动态变化见图5。

### 3 讨论

本研究结果发现, 与NDC组相比, DC组肉芽组织生长率和创面愈合率低, 创面完全愈合时间更长, 愈合过程肉芽组织miR21、miR126、miR146a及miR210低表达, miR29a和miR155高表达, 这可能是糖尿病慢性皮肤溃疡更难愈合的原因之一。与糖尿病慢性创面常规治疗相比, 芦荟凝胶每日治疗及隔日治疗均能明显缩短创面愈合所需时间。与AVG QOD组相比, AVG QD组愈合率较

低、完全愈合时间更长, 可能与每日更换内层芦荟凝胶敷料导致上皮爬行损伤有关。综上, 芦荟凝胶缩短了糖尿病慢性创面愈合时间, 与既往研究结果证实芦荟凝胶促进创面愈合相一致<sup>[22-23]</sup>。

芦荟凝胶促进创面修复的机制尚未完全阐明, 既往研究多从调节大分子层面报道芦荟凝胶促进愈合的机制<sup>[13-16]</sup>, 如下调肿瘤坏死因子- $\alpha$  (TNF- $\alpha$ )、白介素-6 (IL-6)、C-反应蛋白 (CRP) 等炎症介质以减轻炎症反应, 增加巨噬细胞数量以提高炎症反应的速度和质量, 减少淋巴细胞数量缩短炎症的持续时间; 刺激成纤维细胞分泌角质细胞形成因子-1 (KGF-1)、血管内皮生长因子 (VEGF)、转化生长因子- $\beta$  (TGF- $\beta$  1) 和细胞外基质成分 (胶原、糖胺聚糖类物质) 等, 下调基质金属蛋白酶-9 (MMP-9) 与金属蛋白酶组织抑制剂-1 (TIMP-1) 的比值从而调节细胞外基质的生成与降解等。而本研究以miRNAs作为切入点, 探讨芦荟凝胶调控miRNAs促进创面愈合的相关机制。

miR21具有促进抗炎介质IL-10生成, 减少炎症介质TNF $\alpha$ 生成<sup>[24]</sup>; 靶向抑制TIMP3、TIAM1, 促进角质细胞迁移和再上皮化<sup>[25]</sup>; 促进上皮间质转化 (EMT), 促使表皮细

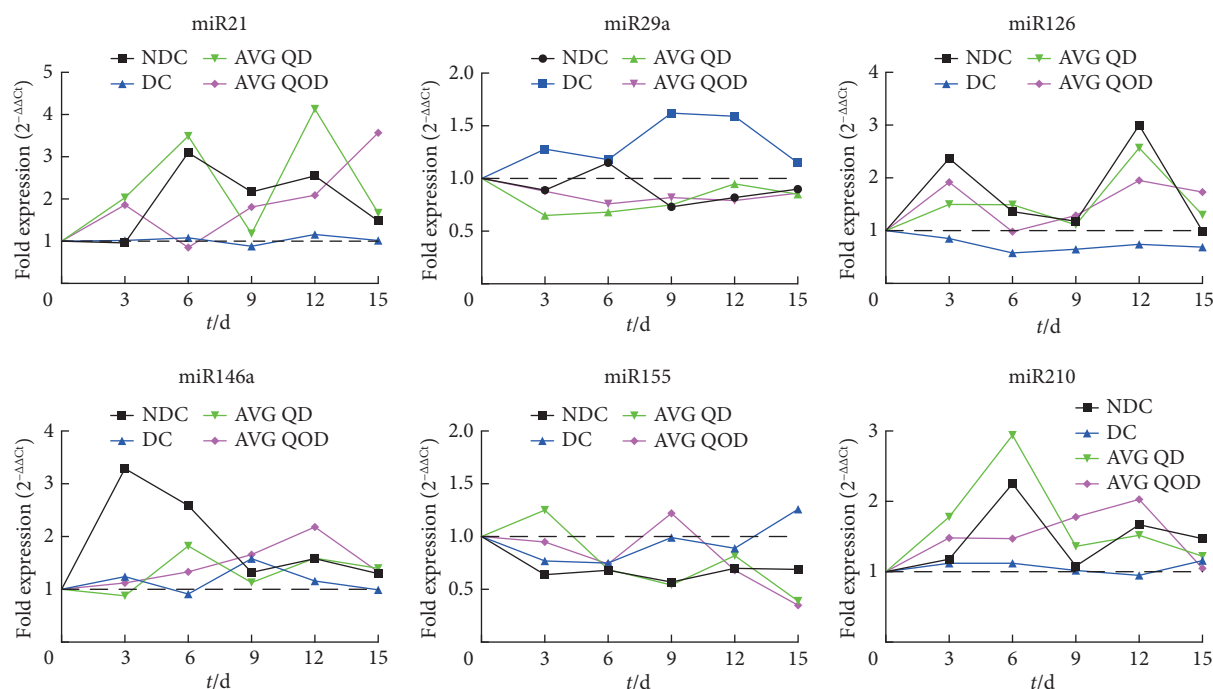


图 5 不同组别间肉芽组织miRNA相对表达量随治疗时间改变的动态变化

Fig 5 Dynamic changes in the relative expression of miRNA in granulation tissues in different groups over the course of treatment

胞转化为成纤维和肌成纤维细胞<sup>[26]</sup>;刺激成纤维细胞增殖分泌TGF- $\beta$ 1、KGF-1等生长因子<sup>[27]</sup>等促进创面愈合,本研究结果显示NDC组、AVG QD组、AVG QOD组miR21表达较DC组显著增高,提示糖尿病对照组创面延迟愈合可能由于肉芽组织miR21表达下调所致,而AVG通过上调创面miR21表达,进而减轻炎症、促进角质细胞迁移与再上皮化以及上皮间质转化等加速创面愈合。

miR29a表达下调, COL1A1、COL3A1表达增强, I型、III型胶原生成增多<sup>[28]</sup>;而miR29a表达上调能够下调TIMP-1、增加功能性MMP-1分泌,降解胶原蛋白,逆转成纤维细胞的促纤维化表型<sup>[29]</sup>。本研究结果显示DC组miR29a表达较NDC组、AVG QD组、AVG QOD组显著增高,AVG下调组织miR29a表达;天狼猩红结果显示治疗初期创面组织I型胶原明显增多,胶原排列致密有序,提示芦荟凝胶通过下调miR29a表达,增加胶原形成、改善胶原重塑。

miR126是抑制VEGF信号通路的负调控因子,促进VEGF信号转导,从而维持血管内皮功能稳定、血管壁完整及新生血管形成<sup>[30]</sup>;芦荟多糖可以通过上调VEGF的表达和VEGFR-2的磷酸化刺激血管内皮细胞迁移、增殖<sup>[31]</sup>。本研究结果显示DC组创面miR126表达下调可能是阻碍其愈合的机制之一,而芦荟凝胶治疗上调miR126表达,促进新生血管形成,从而达到加速创面愈合目的。

miR146a表达下调导致糖尿病创面广泛而持久的异

常炎症反应,间充质干细胞治疗可上调miR146a表达,显著下调炎症因子从而减弱炎症反应,促进伤口修复<sup>[32]</sup>。本研究结果显示DC组miR146a表达与AVG QD组、AVG QOD组无显著差异,提示DC组创面miR146a表达下调可能导致创面愈合延迟;而芦荟凝胶加速创面愈合的机制与miR146a调控无关。

miR155表达下调,可以减少炎症介质TNF- $\alpha$ 、IL-1 $\beta$ ,增加抗炎介质IL-10;通过上调MMP-2、下调TIMP-1水平加速角质形成细胞迁移,减轻胶原沉积,改善胶原排列,减轻纤维化程度<sup>[33-34]</sup>。本研究结果显示AVG QD组及AVG QOD组miR155表达均较DC组显著下调,AVG治疗至创面完全愈合时以III型胶原增加为主,瘢痕成熟过程中又被I型胶原替代,瘢痕印迹小,瘢痕处皮肤光滑,质地柔软。提示芦荟凝胶治疗下调组织miR155表达,可能减轻炎症,改善胶原沉积,减轻瘢痕形成。

miR210在缺氧条件下上调可介导新生毛细血管形成和血管内皮细胞对VEGF的趋化反应<sup>[35]</sup>。本研究结果显示NDC组、AVG QD组及AVG QOD组组织miR210表达均较DC组均显著上调。提示DC组创面miR210表达的下调可能阻碍了创面愈合;给予芦荟凝胶治疗,通过上调miR210表达,促进新生毛细血管形成和血管内皮细胞对VEGF的趋化反应,进而促进糖尿病慢性创面愈合。

本研究不足之处:①为避免治疗期间创面之间药物的相互干扰,实验分组时将模型猪当作一个整体,无法避

免个体差异导致的误差,加之每个实验动物创面数不同,可能影响实验动物全身功能状态,对实验结果产生一定影响;因实验动物数量有限,隔日治疗组创面数仅为每日治疗组的一半。②本研究中糖尿病慢性皮肤溃疡的微环境与临床上合并周围血管病变、神经损害、感染的糖尿病足还存在一定差异,所得结论还需要后续的临床研究补充论证。③本研究虽证实芦荟凝胶能够通过调节miRNAs发挥促愈合作用,但miRNAs完整的机制通路还有待更进一步的基础实验补充。此外,芦荟凝胶配方中各活性成分的不同作用也有待更深入的研究。

与糖尿病常规治疗相比,芦荟凝胶治疗可以缩短创面完全愈合时间,促进创面愈合,隔日治疗组完全愈合时间快于每日治疗组,且未发现不良反应。芦荟凝胶治疗有改善胶原沉积,减轻瘢痕形成的作用。芦荟凝胶治疗可上调创面肉芽组织中miR21、miR126、miR210表达,降低miR29a、miR155表达,这可能是芦荟凝胶促进糖尿病慢性创面愈合、减轻瘢痕的机制之一。

\* \* \*

**利益冲突** 所有作者均声明不存在利益冲突

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