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重组人表皮生长因子凝胶联合赛肤润对慢性伤口患者疼痛评分及不良反应的影响*

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摘要 目的:探讨重组人表皮生长因子(Recombinant human epidermal growth factor,rhEGF)凝胶联合赛肤润对慢性伤口患者疗效及对疼痛评分与不良反应的影响。**方法:**2017 年 3 月 -2019 年 9 月选择在本院进行诊治的胃肠外科术后慢性伤口患者 108 例,根据治疗方法分为联合组与对照组各 54 例。对照组给予赛肤润治疗,联合组在对照组治疗的基础上给予 rhEGF 凝胶治疗,两组都持续给药观察 14 d,记录患者疼痛与不良反应情况。**结果:**联合组治疗第 3 d、第 7 d、第 14 d 的疼痛 VAS 评分都低于对照组(P<0.05)。联合组治疗期间的皮肤坏死、伤口感染、发热等不良反应发生率为 3.7 %,低于对照 18.5 %(P<0.05)。联合组治疗后第 3 d 伤口愈合率为 83.3 %,高于对照组的 59.3 %(P<0.05),治疗后第 7 d、第 14 d 的联合组伤口愈合率稍高于对照组,对比无统计学意义(P>0.05)。两组治疗后的血清血管内皮生长因子(vascular endothelial growth factor,VEGF)含量高于治疗前(P<0.05),联合组高于对照组(P<0.05)。**结论:**rhEGF 凝胶联合赛肤润在慢性伤口患者的应用能促进缓解疼痛评分,减少不良反应的发生,促进 VEGF 的表达,从而加快伤口愈合。

关键词:重组人表皮生长因子凝胶;赛肤润;慢性伤口;疼痛;不良反应

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Effect of Recombinant Human Epidermal Growth Factor Gel Combined with Saifurun on Pain Scores and Adverse Reactions in Patients with Chronic Wounds*

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ABSTRACT Objective: To investigate the effects of recombinant human epidermal growth factor (rhEGF) gel combined with Saifurun on pain scores and adverse reactions in patients with chronic wounds. **Methods:** A total of 108 patients with chronic wounds after gastrointestinal surgery, who were diagnosed and treated in Affiliated Hospital of Xiangnan University from March 2017 to September 2019, were chosen and were divided into combination group(n=54) and control group(n=54). The control group was given Saifurun treatment, and the combination group was given rhEGF gel treatment on the basis of the control group's therapy. The two groups were given continuous administration for 14 days, and the pain and adverse reactions were recorded. **Results:** The pain VAS scores on the 3rd, 7th, and 14th days after treatment of the combination group were lower than those of the control group(P<0.05). The incidence (3.7 %) of skin necrosis, wound infection, fever and other adverse reactions during treatment in the combination group was lower than that (18.5 %) in the control group (P<0.05). The wound healing rates of the combination group on the 3rd, 7th, and 14th days were 83.3 %, 96.3 % and 100.0 %, which were higher than those (59.3 %, 83.3 % and 88.9 %) of the control group (P<0.05). The serum vascular endothelial growth factor (VEGF) levels after treatment in the two groups were higher than those before treatment (P<0.05), and the combination group was higher than the control group (P<0.05). **Conclusion:** The application of rhEGF gel combined with Saifurun in the patients with chronic wounds can promote pain relief scores, reduce the occurrence of adverse reactions, promote the expression of VEGF, and accelerate wound healing.

Key words: Recombinant human epidermal growth factor gel; Saifurun; Chronic wound; Pain; Adverse reactions

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前言

胃肠外科术后伤口易出现愈合不良，如处理不当将严重影响患者康复[1]。现代研究显示外科术后伤口不愈合多与肥胖、医源性环境因素、贫血、术中出血多等因素有关，特别很多术后伤口部位血液供应较差，为此在临床上容易发生伤口不愈合[2,3]。赛肤润是一种液体辅料，含有人体必要的脂肪酸、维生素 E 等，能通过分子置换发挥作用，可增加皮肤的营养及局部组织的抵抗力，促使粘膜上皮细胞分裂增殖加速，促进受伤皮肤的修复[4]。同时能形成一层脂质保护膜，防止皮肤干燥，加速表皮细胞的修复[5,6]。重组人表皮生长因子是利用基因重组技术人工合成的促进伤口修复的生长因子，能促进基质胶原的合成，改善血液循环，促进血肿的吸收和机化，从而能有效促进溃疡伤口的愈合[7-9]。而 rhEGF 凝胶具有较好的分散压力、良好组织相容性，能够吸收患者渗液及汗液，也可增加局部皮肤的携氧能力，当前在临床上应用比较多见[10,11]。本文具体探讨了 rhEGF 凝胶联合赛肤润对慢性伤口患者疼痛评分及不良反应的影响，以明确两者联合使用的价值。现总结报道如下。

1 资料与方法

1.1 研究对象

2017 年 3 月 -2019 年 9 月选择在本院进行诊治的胃肠外科术后慢性伤口患者 108 例，纳入标准：顺利完成手术，均为感染所致慢性伤口，有创面形成；患者签署了知情同意书；本院伦理委员会批准了此次研究；年龄 20~70 岁；男女不限。排除标准：合并有糖尿病的患者；合并有严重心脑血管、肝、肾功能不全等原发疾病；过敏体质者或对本药物过敏者；精神疾病患者。根据治疗方法分为联合组与对照组各 54 例，两组的一般资料对比无差异(P>0.05)，见表 1。

表 1 两组一般资料对比

Table 1 Comparison of general data between two groups

Groups	n	Maximum wound diameter (cm)	Course of wound (weeks)	Gender (M/F)	Surgical site (stomach/colon/rectal)	Age (years)	BMI(kg/m^2)
Joint Group	54	4.14± 0.25	13.07± 1.47	28/26	22/18/14	45.67± 1.47	22.16± 1.57
Control group	54	4.18± 0.33	13.11± 1.11	30/24	21/19/14	45.98± 2.84	22.87± 1.11

1.2 治疗方法

两组入院后给予标准清创处理，清创后以 0.25 %碘伏浸浴处理 1 h，选择生理盐水冲洗 3~5 min，根据伤口恢复情况隔日换药治疗 1 次。

对照组：给予赛肤润治疗，在每日睡前使用赛肤润液体喷剂 (法国优格公司，20 mL/ 瓶，国食药监械 (进) 字 2014 第 3643656)。直接喷于伤口部位，1~2 mL/ 次。

联合组：在对照组治疗的基础上给予 rhEGF 凝胶治疗，将 2 000 IU/mL 的 rhEGF (金深圳化生元基因工程发展有限公司，批号：20010038)直接湿敷于伤口上，隔日换药治疗 1 次。

两组都持续给药观察 14 d。

1.3 观察指标

(1)在治疗后第 3 d、第 7 d、第 14 d 采用视觉模拟评分法 (VAS)评定患者的疼痛状况，分数越高，疼痛越严重。0 分：无痛；7~10 分：有逐渐强烈的疼痛，影响食欲及睡眠，难以忍受。(2)记录两组在治疗期间出现的不良反应情况，主要包括皮肤坏死、伤口感染、发热等。(3)在治疗后第 3 d、第 7 d、第 14 d 计算伤口愈合率，伤口愈合率(%)=(伤口面积 - 残余伤口面积)/ 伤口面积× 100 %。(4)所有患者在治疗前后抽取肘静脉血 2~3 mL。3000 r/min 离心 10 min，取血清。采用酶联免疫法检测血 VEGF 含量，试剂盒购买于上海生工。

1.4 统计方法

应用 SPSS 25.00，计量数据选择 $\bar{x}\pm s$ 示，组间进行独立样本 t 检验，组内比较采用配对 t 检验和重复测量方差分析，计数数据采用率与百分比表示(对比为卡方分析)，以 P<0.05 为差异有统计学意义。

2 结果

2.1 疼痛评分对比

两组治疗后第 3 d、第 7 d、第 14 d 的疼痛 VAS 评分均降低(P<0.05)，联合组治疗后第 3 d、第 7 d、第 14 d 的疼痛 VAS 评分都低于对照组(P<0.05)，见表 2。

表 2 两组治疗后不同时间点的疼痛评分对比(分，$\bar{x}\pm s$)

Table 2 Comparison of pain scores between two groups at different time points after treatment (scores, $\bar{x}\pm s$)

Groups	n	Treatment 3 d	Treatment 7 d	Treatment 14 d
Joint Group	54	4.33± 0.22*	2.84± 0.18*$^{\#}$	1.23± 0.32*$^{\#\&}$
Control group	54	6.59± 0.18	4.19± 0.17$^{\#}$	2.65± 0.17$^{\#\&}$

Note: * P<0.05 compared with the control group, $^{\#}P$<0.05 compared with the treatment 3 d, $^{\&}P$<0.05 compared with the treatment 7 d.

2.2 不良反应情况对比

联合组治疗期间的皮肤坏死、伤口感染、发热等不良反应发生率为 3.7 %，低于对照组的 18.5 %(P<0.05)，见表 3。

表 3 两组治疗期间不良反应情况对比(例,%)

Table 3 Comparison of adverse reactions between two groups during treatment (n, %)

Groups	n	Cutaneous necrosis	Wound infection	Fever	Total
Joint Group	54	0	1	1	2(3.7)*
Control group	54	3	3	4	10(18.5)

Note: *P<0.05 compared with the control group.

2.3 伤口愈合率对比

联合组治疗后第 3 d 伤口愈合率为 83.3 %,高于对照组的 59.3 %(P<0.05),治疗后第 7 d、第 14 d 的联合组伤口愈合率稍高于对照组,对比无统计学意义(P>0.05),见表 4。

表 4 两组治疗后不同时间点的伤口愈合率对比(例,%)

Table 4 Comparison of wound healing rates at different time points after treatment between two groups (n, %)

Groups	n	Treatment 3 d	Treatment 7 d	Treatment 14 d
Joint Group	54	45(83.3)*	50(92.59)	52(96.30)
Control group	54	32(59.3)	45(83.3)	48(88.9)

Note: *P<0.05 compared with the control group.

2.4 VEGF 表达变化对比

两组治疗后的血清 VEGF 含量高于治疗前(P<0.05),联合组高于对照组(P<0.05),见表 5。

表 5 两组治疗前后血清 VEGF 表达变化对比(ng/mL, $\bar{x}\pm s$)

Table 5 Comparison of serum VEGF expression levels before and after treatment between two groups (ng/mL, $\bar{x}\pm s$)

Groups	n	Pretherapy	Post-treatment
Joint Group	54	46.29± 5.69	138.03± 15.39#*
Control group	54	46.18± 3.58	96.40± 8.38#

Note: Compared with before treatment, #P<0.05; Compared with the control group, *P<0.05.

3 讨论

术后慢性伤口愈合是一个比较复杂的病理及生理学过程,许多因素如局部缺血、伤口坏死、伤口污染、炎症反应、异物刺激等可加重这一过程[12]。慢性伤口的发生与发展包括炎症期、细胞增殖期及组织塑形期等,采用清创缝合技术可进行无创缝合,但是毕竟为一种再次手术操作,对患者有一定的创伤[13,14]。赛肤润是一种液体敷料,其中的亚油酸、亚麻酸等占成分中的 99 %左右,另外添加 1 %的茴香作为辅料[15]。赛肤润在皮肤表面形成一层脂质保护膜,能够改善皮肤局部微循环,增加循环血量;其能营养皮肤,有效保持皮肤内水分,增加局部皮肤的氧供,加速损伤部位的修复;同时其可以缓解皮肤干燥等症状,临床应用安全性比较高[16]。rhEGF 广泛存在于人体各组织中,是一种由 53 个氨基酸残基组成的小分子蛋白,能促进细胞分裂与增殖[17,18]。但是二者在慢性伤口创面的的联合应用报道较少,本研究将二者联合应用,显示联合组治疗后第 3 d、第 7 d、第 14 d 的疼痛 VAS 评分都低于对照组;联合组治疗期间的皮肤坏死、伤口感染、发热等不良反应发生率为 3.7 %,低于对照组的 18.5 %。国内外目前没有类似的研究,本研究创新的将 rhEGF 凝胶和赛肤润联合应用于慢性伤口恢复的治疗,取得了较好的疗效,分析其原因为 rhEGF 能够促进蛋白合成与伤口愈合,控制伤口感染,有利于促使伤口早期愈合[19,20]。而采用 rhEGF 凝胶的应用对受压部位有一定的减压及按摩作用,并且具有阻隔细菌和防水的效果,可以减轻摩擦力对皮肤的损伤,从而促进并缓解患者的疼痛症状,减少不良反应的发生[21,22]。

慢性伤口往往长期处于潮湿环境状态下,容易导致皮肤表皮层发白、起皱,使得伤口愈合不良[23]。本研究显示联合组治疗后第 3 d 伤口愈合率为 83.3 %,高于对照组的 59.3 %,治疗后第 7 d、第 14 d 的联合组伤口愈合率稍高于对照组,对比无统计学意义。从机制上分析,赛肤润可增强皮肤营养,锁住皮肤中的水分;也能在皮肤表面形成一层脂质保护膜,加快受损皮肤的修复速度,改善皮肤的微循环[24]。rhEGF 作为趋化因子,能刺激皮肤上皮细胞、成纤维细胞和角质细胞的增殖与迁移,促进核酸、蛋白质的合成,从而有利于伤口的愈合[25]。当前有学者将 rhEGF 应用于治疗颌面部外伤,能缩短恢复时间并减少术后伤口瘢痕增生发生,并最大限度地修复美化伤口、恢复面部功能和形态[26,27]。

rhEGF 可以促进细胞的分裂,同时还能促进羟脯氨酸、透明质酸、纤维连接蛋白等基质的合成。并且其能通过作用于细胞生长调节基因,调节细胞糖酵解及钙离子浓度,促进核酸的修复和蛋白质的合成,从而加速伤口愈合速度[28,29]。本研究显示联合组治疗后的血清 VEGF 含量高于对照组。从机制上分析,血管新生是伤口愈合的必要条件,VEGF 是一种可特异性作用于血管内皮细胞的多功能细胞因子,又称血管通透因子,能增加微血管的通透性,也能促使微血管内皮细胞增殖、迁移,有利于新生血管生长[30]。rhEGF 的应用能促进 VEGF 的合成,能保

证伤口所需要营养和氧分，从而促进新生毛细血管的生成[31]。本研究也存在一定的不足，没有进行随访分析，且没有设置rhEGF单独治疗组，将在后续研究中探讨。

总之，rhEGF凝胶联合赛肤润在慢性伤口患者的应用能促进缓解疼痛评分，减少不良反应的发生，促进VEGF的表达，从而加快伤口愈合。

参考文献(References)

[1] Agunbiade TA, Zaghlol RY, Barac A. Heart Failure in Relation to Tumor-Targeted Therapies and Immunotherapies[J]. Methodist Debakey Cardiovasc J, 2019, 15(4): 250-257

[2] Bashir AIJ, Kankipati CS, Jones S, et al. A novel mechanism for the anticancer activity of aspirin and salicylates [J]. Int J Oncol, 2019, 54 (4): 1256-1270

[3] Chinuki Y, Morita E. Alpha-Gal-containing biologics and anaphylaxis [J]. Allergol Int, 2019, 68(3): 296-300

[4] 夏杰,段霞,曹程秀,等.赛肤润及安普贴在护理人员鼻面部压力性损伤预防中的应用[J].护理研究, 2020, 34(16): 2977-2979

[5] 邓宝贵,谢裕华,全小明,等.中药乐肤佳局部涂擦对1期压力性损伤的干预疗效观察[J].广州中医药大学学报, 2020, 37(3): 432-437

[6] 乔敏.造口护肤粉联合3M液体敷料治疗在新生儿重度臀红中的应用[J].国际护理学杂志, 2020, 39(8): 1443-1445

[7] Dwivedi C, Pandey H, Pandey AC, et al. In Vivo Biocompatibility of Electrospun Biodegradable Dual Carrier (Antibiotic + Growth Factor) in a Mouse Model-Implications for Rapid Wound Healing [J]. Biosci Rep, 2019, 11(4): 114-119

[8] Genuino AJ, Chaikledkaew U, The DO, et al. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis[J]. IUBMB Life, 2019, 12(8): 815-824

[9] Hutcheon AEK, Zieske JD, Guo X, et al. Wound Healing Potential of Low Temperature Plasma in Human Primary Epidermal Keratinocytes[J]. Sci Rep, 2019, 16(6): 585-593

[10] Jerusalem G. HER2+ breast cancer treatment and cardiotoxicity: monitoring and management[J]. Immunology, 2019, 177(2): 237-250

[11] Kaita Y, Tarui T, Yoshino H, et al. Sufficient therapeutic effect of cryopreserved frozen adipose-derived regenerative cells on burn wounds[J]. J Physiol, 2019, 10(4): 92-103

[12] Kim JB, Yao Q, Yu Z. High Efficient Expression and Purification of Human Epidermal Growth Factor in Arachis Hypogaea L [J]. Tissue Eng Regen Med, 2019, 20(8): 221-229

[13] Kosalka P, Johnson C, Turek M, et al. Effect of obesity, dyslipidemia, and diabetes on trastuzumab-related cardiotoxicity in breast cancer[J]. Curr Oncol, 2019, 26(3): e314-e321

[14] Lancellotti P, Kim SB, Shu DY. Epidermal Growth Factor Stimulates Transforming Growth Factor-Beta Receptor Type II Expression In Corneal Epithelial Cells [J]. Breast Cancer Res Treat, 2019, 9(1): e8079

[15] 孙钰,郭倩,李利铭.蒙脱石散外敷联合赛肤润修复失禁性皮炎患者皮肤损伤的效果[J].护理实践与研究, 2020, 17(12): 138-139

[16] 宋思敏,闫雅凤,赵凯丽,等.赛肤润预防医务人员头面部压力性损伤的早期干预效果[J].解放军医学院学报, 2020, 41(5): 498-501

[17] Lee EJ, Kim JY, Ahn Y, et al. Critical Role of ATP-P2X7 Axis in UV-Induced Melanogenesis [J]. J Invest Dermatol, 2019, 139(7): 1554-1563

[18] Sriwidodo S, Subroto T, Maksum IP, et al. Optimization of Secreted Recombinant Human Epidermal Growth Factor Production Using Pectate Lyase B from Escherichia Coli BL21 (DE3) by Central Composite Design and Its Production in High Cell Density Culture [J]. J Pharm Bioallied Sci, 2019, 11(Suppl 4): S562-s566

[19] Sun J, Zhang Y, Song X, et al. The Healing Effects of Conditioned Medium Derived from Mesenchymal Stem Cells on Radiation-Induced Skin Wounds in Rats [J]. Rev Bras Enferm, 2019, 28(1): 105-115

[20] Sun X, Jia M, Sun W, et al. Functional role of RBM10 in lung adenocarcinoma proliferation[J]. Int J Oncol, 2019, 54(2): 467-478

[21] Takimoto M. Multidisciplinary Roles of LRRFIP1/GCF2 in Human Biological Systems and Diseases[J]. Cells, 2019, 8(2): 332-339

[22] Takimoto M, Ohmori T, Sagara H, et al. TNFα promotes mucosal wound repair through enhanced platelet activating factor receptor signaling in the epithelium[J]. Int J Mol Sci, 2019, 12(4): 909-918

[23] Tu CL, Celli A, Mauro T, et al. Calcium-Sensing Receptor Regulates Epidermal Intracellular Ca(2+) Signaling and Re-Epithelialization after Wounding[J]. Turk J Haematol, 2019, 139(4): 919-929

[24] Uchiyama A, Nayak S, Graf R, et al. SOX2 Epidermal Overexpression Promotes Cutaneous Wound Healing via Activation of EGFR/MEK/ERK Signaling Mediated by EGFR Ligands [J]. J Cell Mol Med, 2019, 139(8): 1809-1820

[25] Wang Q, Liu J, Guo T, et al. Epidermal Growth Factor Reverses the Inhibitory Effects of the Bisphosphonate, Zoledronic Acid, on Human Oral Keratinocytes and Human Vascular Endothelial Cells In Vitro via the Epidermal Growth Factor Receptor (EGFR)/Akt/Phosphoinositide 3-Kinase (PI3K) Signaling Pathway [J]. Med Sci Monit, 2019, 25(9): 700-710

[26] Xie ZB, Zhang YF, Jin C, et al. LRG-1 promotes pancreatic cancer growth and metastasis via modulation of the EGFR/p38 signaling[J]. J Exp Clin Cancer Res, 2019, 38(1): e75

[27] Li F, Bian L, Iriyama S, et al. Smad7 Ameliorates TGF-β-Mediated Skin Inflammation and Associated Wound Healing Defects but Not Susceptibility to Experimental Skin Carcinogenesis [J]. J Clin Med, 2019, 139(4): 940-950

[28] Liu P, Zheng H, Xu Y, et al. Preparation and in vivo evaluation of a topical hydrogel system incorporating highly skin-permeable growth factors, quercetin, and oxygen carriers for enhanced diabetic wound-healing therapy[J]. Int J Mol Sci, 2019, 14(4): 5449-5475

[29] Luo X, He Y, Tang H, et al. Effects of HER2 on the invasion and migration of gastric cancer [J]. Am J Transl Res, 2019, 11(12): 7604-7613

[30] Nowak D, Nakano MH, Udagawa C, et al. A Genome-Wide Association Study Identifies Five Novel Genetic Markers for Trastuzumab-Induced Cardiotoxicity in Japanese Population [J]. Int J Mol Sci, 2019, 42(12): 2045-2053

[31] Palamidessi A, Malinverno C. Unjamming overcomes kinetic and proliferation arrest in terminally differentiated cells and promotes collective motility of carcinoma [J]. Pharmaceutics, 2019, 18(11): 1252-1263