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A 型肉毒素与复方倍他米松注射液联用治疗瘢痕疙瘩患者的疗效及安全性研究 *

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摘要 目的:分析 A 型肉毒素与复方倍他米松注射液联用治疗瘢痕疙瘩患者的疗效及安全性。**方法:**选取 2015 年 1 月 -2016 年 8 月期间我院收治的 90 例瘢痕疙瘩患者为研究对象,根据治疗方法将患者随机分为 A 组、B 组和 C 组各 30 例。A 组给予 A 型肉毒素治疗,B 组给予复方倍他米松注射液治疗,C 组给予 A 型肉毒素联合复方倍他米松注射液治疗。比较三组患者的相关指标改善评分、临床疗效、不良反应发生率和复发率。**结果:**C 组患者体积、痛痒觉、硬度和自我评价的改善评分均高于 B 组和 A 组(P<0.05),B 组的各项指标改善评分和 A 组相比差异无统计学意义(P>0.05)。三组总有效率比较差异有统计学意义,且 C 组高于 B 组(P<0.05),A 组和 C 组总有效率比较差异无统计学意义(P>0.05)。A 组不良反应总发生率低于 B 组和 C 组,差异有统计学意义(P<0.05),B 组与 C 组不良反应总发生率相比,差异无统计学意义(P>0.05)。A 组和 C 组治疗后半年、1 年瘢痕疙瘩复发率均低于 B 组(P<0.05),但 A 组和 C 组比较差异无统计学意义(P>0.05)。**结论:**与单独使用 A 型肉毒素或复方倍他米松注射液相比,A 型肉毒素与复方倍他米松注射液联合使用治疗瘢痕疙瘩能显著提高疗效,降低复发率,且不会增加不良反应发生率,安全性较高,值得进一步推广应用。

关键词:A 型肉毒素;复方倍他米松注射液;瘢痕疙瘩;疗效;安全性

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Research of Efficacy and Safety of Botulinum Toxin Type A Combined with Compound Betamethasone Injection in Treatment of Patients with Keloid*

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ABSTRACT Objective: To analyze the efficacy and safety of botulinum toxin type A combined with compound betamethasone injection in treatment of patients with keloid. **Methods:** 90 patients with keloid who were treated in our hospital from January 2015 to August 2016 were selected as the research object, and they were randomly divided into A group, B group and C group according to different of treatment methods, 30 cases in each group. The A group were treated with botulinum toxin type A, the B group were treated with compound betamethasone injection and the C group were treated with botulinum toxin type A combined with compound betamethasone injection. Related indexes improvement score, clinical efficacy, the incidence of adverse reaction and the recurrence rate were compared between three groups. **Results:** The improvement score of keloid volume, hardness, pain/itching sensation and self-evaluation of patients in C group were higher than those in B group and A group (P<0.05). There was no statistical difference in improvement score of various indexes between the B group and the A group (P>0.05). The total effective rate of the three groups was statistically significant,and the C group was higher than that of the B group (P<0.05). There was no significant difference in the total effective rate between the A group and the C group (P>0.05). The total incidence of adverse reactions in A group was lower than those in B group and C group, the difference was statistically significant (P<0.05), while there was no difference between B group and C group (P>0.05). The recurrence rate of keloid in A group and C group was lower than that in B group at half a year and 1 years after treatment(P<0.05), but there was no significant difference between A group and C group (P>0.05). **Conclusion:** Compared with the use of botulinum toxin type A or compound betamethasone injection alone, the combined use of botulinum toxin type A and compound betamethasone injection in the treatment of keloid can significantly improve the efficacy, reduce the recurrence rate, and it does not increase the incidence of adverse reactions, safety is high, which is worthy of further application.

Key words: Botulinum toxin type A; Compound betamethasone injection; Keloid; Efficacy; Safety

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前言

瘢痕疙瘩是由细胞外基质成分沉积增加引起的一种皮肤纤维化疾病，具有一定的遗传易感性和家族倾向性等特点[1,2]。瘢痕疙瘩常有疼痛和瘙痒症状，如位于关节等部位会限制关节活动功能，严重影响患者的日常工作和生活质量[3,4]。目前瘢痕疙瘩的主要治疗方法是向皮损内注射糖皮质激素，但是随着临床实践的积累和患者对医疗质量需求的提升，仅通过皮损内注射糖皮质激素难以满足治疗需求，疗效不佳，以致有部分疼痛、瘙痒严重的患者经激素注射治疗后症状未见明显改善，且容易复发[5-7]。近年，国内外研究报道表明[8,9]，A 型肉毒素能够抑制乙酰胆碱的释放，使肌纤维松弛，进而可以抑制瘢痕疙瘩成纤维细胞的增殖，从而减少瘢痕的形成。复方倍他米松注射液通过减少生长因子的生成、抑制成纤维细胞的增生发挥作用，与此同时，其还具有良好的抗炎作用[10]。因此本研究选用 A 型肉毒素和复方倍他米松注射液两种药物，研究两者单独使用和联合使用对瘢痕疙瘩的效果，并评价其疗效及其安全性。

1 资料与方法

1.1 一般资料

选取 2015 年 1 月 -2016 年 8 月期间我院收治的 90 例瘢痕疙瘩患者为研究对象，纳入标准：(1)患者满足瘢痕疙瘩的相关诊断标准[11]，皮损向周围皮肤侵犯超出原先的皮损范围或病程超过 9 个月仍无自行消退可能；(2) 患者痛痒症状明显；(3) 入组患者了解了本研究的目的及过程，签署知情同意书并遵嘱治疗。排除标准：(1)3 个月内接受过药物治疗、光疗或冷冻治疗的患者；(2)2 年内接受过放疗的患者；(3) 皮损内存在感染者；(4)合并有严重内科疾病、肿瘤或内分泌系统疾病者；(5)妊娠期或哺乳期女性患者；(6)伴有精神疾病，依从性差者。根据治疗方法随机分为 A 组、B 组和 C 组各 30 例。A 组男 19 例，女 11 例；年龄 18-50 岁，平均(29.76± 4.98)岁；病程 1-19 年，平均(6.32± 1.89)年；四肢皮损 9 例，躯干皮损 21 例。B 组男 18 例，女 12 例；年龄 21-53 岁，平均(30.18± 5.35)岁；病程 2-17 年，平均(5.82± 2.10)年；四肢皮损 11 例，躯干皮损 19 例。C 组男 21 例，女 9 例；年龄 17-51 岁，平均(29.57± 5.15)岁；病程 1-20 年，平均(6.13± 1.76)年；四肢皮损 10 例，躯干皮损 20 例。三组患者性别、年龄、病程、病变部位之间对比，差异无统计学意义(P>0.05)，具有可比性。本研究经我院伦理委员会审查通过。

1.2 治疗方法

A 组给予注射用 A 型肉毒毒素（兰州生物制品研究所有限公司，批准文号：国药准字 S10970037)进行瘢痕疙瘩皮损内注射，以 2.5 mL 0.9%生理盐水将其用稀释至浓度为 50 U/mL，随后将稀释药液缓缓注入瘢痕实质内，当瘢痕出现明显的膨隆状，外观呈现苍白色和橘皮样时，说明药液开始向周围浸润，此时结束注射，仅注射一次。B 组、C 组给予复方倍他米松注射液（上海先灵葆雅制药有限公司，批准文号：国药准字 J20130084）进行瘢痕疙瘩皮损内注射，注射剂量为 0.2 mL/cm^3，每人每次注射量不超过 1 mL，患者每 4 周注射 1 次，连续 3 次。C 组在首次注射复方倍他米松注射液后，即刻向瘢痕疙瘩实质中注射 A 型肉毒毒素，方法参照 A 组。B 组和 C 组疗程均为 3 个月。

1.3 评价指标

相关指标评价：观察三组患者治疗前后瘢痕疙瘩体积、硬度、痛痒觉和自我评价的改善评分。评分标准[12]：各指标改善评分分成 4 个区间，体积改善评分：3 分：改善 >60%；2 分：改善 40%-60%；1 分：改善 20%-40%；0 分：改善 <20%。硬度改善评分：3 分：改善 >42%；2 分：改善 28%-42%；1 分：改善 14%-28%；0 分：改善 <14%。痛痒觉改善评分：3 分：改善 >63%；2 分：改善 42%-63%；1 分：改善 21%-42%；0 分：改善 <21%。自我评价改善评分：3 分：改善 >66%；2 分：改善 44%-66%；1 分：改善 22%-44%；0 分：改善 <22%。

疗效评价：根据上述指标改善评分总和将疗效分为痊愈、显效、有效和无效 4 个等级。总评分 10-12 分记为痊愈；总评分为 7-9 分记为显效；总评分为 4-6 分记为有效；总评分 <3 分记为无效。总有效率 =(痊愈 + 显效 + 有效)/ 总例数× 100%。

不良反应评价：记录治疗过程中三组出现的各种不良反应，包括疼痛、水肿、红肿和灼热等。

疾病复发评判标准：在治疗后半年和治疗后 1 年患者出现如下现象认定为复发，瘢痕瘙痒加重、质地变硬、瘢痕体积变大等。

1.4 统计学方法

采用 SPSS19.0 统计学软件进行数据统计，年龄、相关指标改善评分计量资料以($\bar{x}$± s)表示，组间比较采用 t 检验，临床疗效、不良反应发生率、复发率、性别构成等计数资料以率(%)表示，比较采用 χ^2 检验，将 α=0.05 作为检验标准。

2 结果

2.1 三组患者相关指标改善评分对比

三组患者在体积、痛痒觉、硬度和自我评价的改善评分整体比较，差异均有统计学意义(P<0.05)。C 组患者的各项指标改善评分均高于 B 组和 A 组(P<0.05)，B 组的各项指标改善评分和 A 组相比差异无统计学意义(P>0.05)。具体见表 1。

表 1 三组患者相关指标改善评分对比(分，$\bar{x}$± s)

Table 1 Comparison of improvement score of related indexes of patients in three groups (scores, $\bar{x}$± s)

Groups	n	Keloid volume	Hardness	Itching sensation	Self evaluation
A group	30	1.78± 0.71	1.75± 0.39	2.05± 0.28	1.86± 0.67
B group	30	1.31± 0.57	1.47± 0.51	1.85± 0.37	1.65± 0.46
C group	30	2.87± 0.63^{ab}	2.75± 0.46^{ab}	2.47± 0.41^{ab}	2.78± 0.57^{ab}
F		4.356	3.985	2.998	5.455
P		0.037	0.043	0.047	0.026

Note: Comparison of A group, ^{a}P<0.05; comparison of B group, ^{b}P<0.05.

2.2 三组患者临床疗效对比

三组总有效率比较差异有统计学意义，且 C 组高于 B 组（P<0.05），A 组和 C 组总有效率比较差异无统计学意义（P>0.05）。具体见表 2。

表 2 三组患者临床疗效对比[n(%)]

Table 2 Comparison of the clinical efficiency of patients in three groups[n(%)]

Groups	n	Cure	Excellence	Effective	Invalid	Total effective rate
A group	30	19(63.33)	5(16.67)	3(10.00)	3(10.00)	27(90.00)
B group	30	16(53.33)	4(13.33)	2(6.67)	8(26.67)	22(73.33)
C group	30	24(80.00)	3(10.00)	2(6.67)	1(3.33)	29(96.67)[a]
x^2						9.756
P						0.018

Note: Comparison of B group, [a]P<0.05.

2.3 三组患者不良反应发生率对比

三组不良反应总发生率整体比较差异有统计学意义（P<0.05）。A 组不良反应总发生率低于 B 组和 C 组，差异有统计学意义（P<0.05），B 组与 C 组不良反应总发生率相比，差异无统计学意义（P>0.05）。具体见表 3。

表 3 三组患者不良反应发生率对比[n(%)]

Table 3 Comparison of incidence of adverse reactions of patients in three groups [n(%)]

Groups	n	Pain	Edema	Red and swollen	Scorching hot	Total incidence
A group	30	0(0.00)	0(0.00)	1(3.33)	0(0.00)	1(3.33)
B group	30	3(10.00)	2(6.67)	2(6.67)	4(13.33)	11(36.67)[a]
C group	30	1(3.33)	2(6.67)	3(10.00)	3(10.00)	9(30.00)[a]
x^2						11.329
P						0.004

Note: Comparison of A group, [a]P<0.05.

2.4 三组患者疾病复发率对比

三组间患者治疗后半年、1 年瘢痕疙瘩复发率相比，差异有统计学意义（P<0.05）。A 组和 C 组治疗后半年、1 年瘢痕疙瘩复发率均低于 B 组（P<0.05），但 A 组和 C 组比较差异无统计学意义（P>0.05）。具体见表 4。

表 4 三组患者疾病复发率对比[n(%)]

Table 4 Comparison of the recurrence rate of patients in the three groups [n(%)]

Groups	n	Half a year after treatment	1 years after treatment
A group	30	6(20.00)[a]	9(30.00)[a]
B group	30	14(46.66)	17(56.67)
C group	30	3(10.00)[a]	5(16.67)[a]
x^2		13.561	21.438
P		0.000	0.000

Note: Comparison of B group, [a]P<0.05.

3 讨论

因多种原因导致的皮肤受损后，组织的修复过程中出现纤维组织大量增生和胶原过度沉积，进而形成瘢痕疙瘩，其超出了原本的损伤范围，并累及了附近的皮肤[13-15]。单纯手术治疗瘢痕疙瘩的效果不佳且极易复发，故其主要治疗方法是非手术治疗。国内外通常的非手术治疗方法主要包括药物治疗、压力治疗、冷冻治疗、放疗等，其中皮损内注射药物仍是瘢痕疙瘩的经典治疗方案，至今为止糖皮质激素仍是临床公认的首选注射药物[16-18]。糖皮质激素能够有效促进胶原酶的生成，从而对成纤维细胞的增殖及胶原蛋白的合成起抑制作用，减少胶原酶抑制剂含量，进而有效抑制瘢痕疙瘩生长[19,20]。有研究显示，瘢痕疙瘩患者采用皮损内注射激素治疗后，其皮损程度有所缓解，但皮损厚度、痛痒觉将会在短时间后出现加重症状，因而对于瘢痕疙瘩应根据皮损具体情况采取联合治疗方案[21]。A 型肉毒素是由肉毒杆菌分泌的细菌内毒素，作用于胆碱能运动神经的末

梢,通过拮抗钙离子,减少运动神经末梢乙酰胆碱的释放,抑制肌纤维的收缩功能,使肌肉达到松弛状态,可应用于手术切口边缘,促进创口愈合,减少瘢痕增生,并且 A 型肉毒素在在整形外科领域中有广泛的应用。近年来有报道显示,A 型肉毒素在前列腺增生组织的凋亡调控中起重要促进作用[22-24]。随着研究的深入,学者发现 A 型肉毒素有助于减轻瘢痕疙瘩患者痛痒症状,同时可促进瘢痕组织萎缩,并逐步趋于扁平[25]。

本研究选取 A 型肉毒素和复方倍他米松注射液两种药物,分析二者在瘢痕疙瘩患者治疗上联合应用的效果。结果显示,给予 A 型肉毒素联合复方倍他米松注射液治疗的患者在治疗后瘢痕疙瘩体积、痛痒觉、硬度及自我评价改善评分高于两种药物单独应用,总有效率亦显著提高。说明两种药物联合应用治疗效果较好,其中局部注射复方倍他米松注射液后,其可与特异性受体相结合定位于成纤维细胞的细胞核,通过调节瘢痕相关基因的表达,减少功能性蛋白的合成,抑制成纤维细胞和胶原纤维的合成,减少肉芽组织的生长,促进瘢痕恢复;同时瘢痕皮肤的 C 类神经元的兴奋阈值下调,给予微量刺激便可致使肥大细胞的 5-HT、组胺和 P 物质等释放增加,产生痛痒觉[26]。但是复方倍他米松注射液无法抑制 5-HT、组胺和 P 物质的释放,而 A 型肉毒素可发挥神经毒作用,稳定肥大细胞膜,有效抑制炎症介质和细胞因子的释放,减轻痛痒觉,本研究结果与此观点基本吻合[27]。另外,相关研究显示[28],A 型肉毒素还能够降低成纤维细胞内 TGF-β1 含量,从而缩小瘢痕范围。因此,复方倍他米松注射液和 A 型肉毒素在治疗机制上起到互补作用。其次,笔者发现,所有患者治疗过程中均未出现严重不良反应,复方倍他米松注射液单独应用的 B 组和两药联用的 C 组的不良反应发生率均显著高于单纯给予 A 型肉毒素的 A 组患者,提示不良反应主要由复方倍他米松注射液产生,在 B 组和 C 组的不良反应比较中并未发现有显著统计学差异,提示 A 型肉毒素和复方倍他米松注射液联合使用并未增加不良反应发生率,安全性较高。在多项研究中也证实,A 型肉毒素用于病理性瘢痕的治疗均未出现严重不良反应,可作为瘢痕疙瘩安全有效的防治药物[29,30]。此外,A 组和 C 组治疗后治疗后半年、1 年瘢痕疙瘩复发率均低于 B 组(P<0.05),提示两药联合应用能明显提高瘢痕疙瘩的治疗稳定性,有效降低复发风险。

综上所述,A 型肉毒素与复方倍他米松注射液联合使用治疗瘢痕疙瘩能够显著提高疗效,降低复发率,安全有效,值得临床推广应用。此外,鉴于本研究所含样本量较少,因而还需要通过进一步扩大样本,开展多中心研究来证实。

参 考 文 献(References)

[1] Zhang MZ, Dong XH, Guan EL, et al. A comparison of apoptosis levels in keloid tissue, physiological scars and normal skin [J]. Am J Transl Res, 2017, 9(12): 5548-5557

[2] Jia J, Wang M, Song L, et al. A melanotic malignant melanoma presenting as a keloid: A case report[J]. Medicine (Baltimore), 2017, 96 (49): e9047

[3] Kang SU, Kim YS, Kim YE, et al. Opposite effects of non-thermal plasma on cell migration and collagen production in keloid and normal fibroblasts[J]. PLoS One, 2017, 12(11): e0187978

[4] Aoki M, Akaishi S, Nakao J, et al. Objective Spectrometric Measurement of Keloid Color in the East Asian Population: Pitfalls of Subjective Color Measurements[J]. J Nippon Med Sch, 2016, 83(4): 142-149

[5] Park KY, Lee Y, Hong JY, et al. Vibration Anesthesia for Pain Reduction During Intralesional Steroid Injection for Keloid Treatment [J]. Dermatol Surg, 2017, 43(5): 724-727

[6] Danielsen PL, Rea SM, Wood FM, et al. Verapamil is Less Effective than Triamcinolone for Prevention of Keloid Scar Recurrence After Excision in a Randomized Controlled Trial [J]. Acta Derm Venereol, 2016, 96(6): 774-778

[7] Rutkowski D, Syed F, Matthews LC, et al. An abnormality in glucocorticoid receptor expression differentiates steroid responders from nonresponders in keloid disease [J]. Br J Dermatol, 2015, 173 (3): 690-700

[8] Shaarawy E, Hegazy RA, Abdel Hay RM. Intralesional botulinum toxin type A equally effective and better tolerated than intralesional steroid in the treatment of keloids: a randomized controlled trial[J]. J Cosmet Dermatol, 2015, 14(2): 161-166

[9] 韩笑,谭谦.注射 A 型肉毒毒素预防和治疗病理性瘢痕的研究进展[J].东南大学学报(医学版), 2017, 36(3): 496-500
Han Xiao, Tan Qian. Research Progress on the injection of botulinum toxin A for the prevention and treatment of pathological scar[J]. Journal of Southeast University (Medical Science Edition), 2017, 36(3): 496-500

[10] Zhang YK, Yang H, Zhang JY, et al. Intralesional injection of diprospan is effective for infantile hemangioma [J]. Int J Clin Pract, 2014, 68(5): 633-638

[11] 蔡景龙.瘢痕疙瘩的诊疗指南建议[J].中国美容医学, 2016, 25(6): 38-40
Cai Jing-long. Recommendations for the diagnosis and treatment of keloid[J]. Chinese Journal of Aesthetic Medicine, 2016, 25(6): 38-40

[12] 陈晓明,戴强,施文娟,等.复方倍他米松注射液联合曲安奈德注射液序贯治疗瘢痕疙瘩的有效性和安全性[J].中国医药导报, 2016, 13(35): 24-27
Chen Xiao-ming, Dai Qiang, Shi Wen-juan, et al. Effect and safety of Compound Betamethasone Injection combined with Riamcinolone Acetonide Injection sequential treatment of keloid [J]. China Medical Herald, 2016, 13(35): 24-27

[13] Forbat E, Ali FR, Al-Niaimi F. Treatment of keloid scars using light-, laser- and energy-based devices: a contemporary review of the literature[J]. Lasers Med Sci, 2017, 32(9): 2145-2154

[14] Rang Z, Wang ZY, Pang QY, et al. MiR-181a Targets PHLPP2 to Augment AKT Signaling and Regulate Proliferation and Apoptosis in Human Keloid Fibroblasts [J]. Cell Physiol Biochem, 2016, 40(3-4): 796-806

[15] Lee WJ, Ahn HM, Na Y, et al. Mortalin deficiency suppresses fibrosis and induces apoptosis in keloid spheroids[J]. Sci Rep, 2017, 7(1): 12957

[16] 周毕峰,常宏,石定,等.瘢痕疙瘩的治疗新进展[J].现代生物医学进展, 2016, 16(7): 1394-1397
Zhou Bi-feng, Chang Hong, Shi Ding, et al. The Progress in Keloid Treatment [J]. Progress in Modern Biomedicine, 2016, 16 (7): 1394-1397

[17] Reissis D, Tickunas T, Agha RA, et al. Intralesional excision with topical intralesional cryotherapy improves the treatment of keloid

scarring in a paediatric patient[J]. Ann R Coll Surg Engl, 2017, 99(8): e233-e335

[18] Pozzi M, Zoccali G, Drago MC, et al. Radiotherapy following surgery in keloid treatment: our protocol [J]. G Ital Dermatol Venereol, 2016, 151(5): 492-498

[19] Hsu CK, Lin HH, Harn HI, et al. Caveolin-1 Controls Hyperresponsiveness to Mechanical Stimuli and Fibrogenesis-Associated RUNX2 Activation in Keloid Fibroblasts [J]. J Invest Dermatol, 2018, 138(1): 208-218

[20] Li J, Fu R, Li L, et al. Co-delivery of dexamethasone and green tea polyphenols using electrospun ultrafine fibers for effective treatment of keloid[J]. Pharm Res, 2014, 31(7): 1632-1643

[21] Bijlard E, Steltenpool S, Niessen FB. Intralesional 5-fluorouracil in keloid treatment: a systematic review [J]. Acta Derm Venereol, 2015, 95(7): 778-782

[22] Haubner F, Leyh M, Ohmann E, et al. Effects of botulinum toxin A on patient-specific keloid fibroblasts in vitro[J]. Laryngoscope, 2014, 124(6): 1344-1351

[23] Robinson AJ, Khadim MF, Khan K. Keloid scars and treatment with Botulinum Toxin Type A: the Belfast experience [J]. J Plast Reconstr Aesthet Surg, 2013, 66(3): 439-440

[24] Xiaoxue W, Xi C, Zhibo X. Effects of botulinum toxin type A on expression of genes in keloid fibroblasts[J]. Aesthet Surg J, 2014, 34(1): 154-159

[25] Wilson AM. Eradication of keloids: Surgical excision followed by a single injection of intralesional 5-fluorouracil and botulinum toxin[J]. Can J Plast Surg, 2013, 21(2): 87-91

[26] Van Leeuwen MC, Van der Wal MB, Bulstra AE, et al. Intralesional cryotherapy for treatment of keloid scars: a prospective study[J]. Plast Reconstr Surg, 2015, 135(2): 580-589

[27] 刘爱英,訾绍霞,靳汪洋,等.A 型肉毒毒素在几种皮肤病的应用进展[J].国际皮肤性病学杂志, 2016, 42(3): 184-187
Liu Ai-ying, Zi Shao-xia, Jin Wang-yang, et al. Progress in the application of botulinum toxin type A in several skin diseases [J]. International Journal of Dermatology and Venereology, 2016, 42(3): 184-187

[28] Zhu HY, Bai WD, Li J, et al. Peroxisome proliferator-activated receptor-γ agonist troglitazone suppresses transforming growth factor-β1 signalling through miR-92b upregulation-inhibited Axl expression in human keloid fibroblasts in vitro [J]. Am J Transl Res, 2016, 8(8): 3460-3470

[29] 刘文阁,于波,孙瑛,等.新型药物组合注射治疗瘢痕疙瘩的临床应用初探[J].中华医学美学美容杂志, 2013, 19(6): 460-461
Liu Wen-ge, Yu Bo, Sun Ying, et al. A preliminary study on the clinical application of combined injection of new drugs in the treatment of keloid [J]. Chinese Journal of Medical Aesthetics and Cosmetology, 2013, 19(6): 460-461

[30] 王小玉,王小琴,刘琰,等.面部小面积瘢痕手术切口早期应用 A 型肉毒毒素注射联合强脉冲光照射的临床效果[J].实用皮肤病学杂志, 2013, 6(5): 271-273
Wang Xiao-yu, Wang Xiao-qin, Liu Yan, et al. Effect of incision early combined botulinum toxin type A injections and intense pulsed light treatment for facial small area scar surgery [J]. Journal of Practical Dermatology, 2013, 6(5): 271-273

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[17] Oltean HN, Soliman AS, Omar OS, et al. Risk factors for chronic mastitis in morocco and egypt [J]. International journal of inflammation, 2013, 2013(184921)

[18] Hur SM, Cho DH, Lee SK, et al. Experience of treatment of patients with granulomatous lobular mastitis [J]. Journal of the Korean Surgical Society, 2013, 85(1): 1-6

[19] Kamyab A. Granulomatous lobular mastitis secondary to mycobacterium fortuitum [J]. World journal of clinical cases, 2016, 4(12): 409-412

[20] Gurleyik G, Aktekin A, Aker F, et al. Medical and surgical treatment of idiopathic granulomatous lobular mastitis: A benign inflammatory disease mimicking invasive carcinoma [J]. Journal of breast cancer, 2012, 15(1): 119-123

[21] Scheinfeld N. Diseases associated with hidranitis suppurativa: Part 2 of a series on hidradenitis [J]. Dermatology online journal, 2013, 19 (6): 18558

[22] Al Nazer MA. Idiopathic granulomatus lobular mastitis. A forgotten clinical diagnosis[J]. Saudi medical journal, 2003, 24(12): 1377-1380

[23] Lehman TD, Damania Z, Tschetter CN, et al. Firm, non-tender mass in right breast. Worsening, nonproductive cough. Pleuritic pain. Dx? [J]. The Journal of family practice, 2017, 66(1): 38-41

[24] Holla S, Amberkar MB, Kamath A, et al. Risperidone induced granulomatous mastitis secondary to hyperprolactinemia in a non-pregnant woman-a rare case report in a bipolar disorder [J]. Journal of clinical and diagnostic research: JCDR, 2017, 11(1): FD01-FD03

[25] Yip CH, Jayaram G, Swain M. The value of cytology in granulomatous mastitis: A report of 16 cases from malaysia [J]. The Australian and New Zealand journal of surgery, 2000, 70(2): 103-105

[26] Tolosa T, Verbeke J, Piepers S, et al. Milk production, quality, and consumption in jimma (ethiopia): Facts and producers', retailers', and consumers' perspectives[J]. Preventive veterinary medicine, 2016, 124 (9-14)

[27] Mohammadsadegh M. Impact of intramammary tilmicosin infusion as a dry cow therapy[J]. Journal of veterinary pharmacology and therapeutics, 2018, 41(1): 22-27

[28] Vakkamaki J, Taponen S, Heikkila AM, et al. Bacteriological etiology and treatment of mastitis in finnish dairy herds [J]. Acta veterinaria Scandinavica, 2017, 59(1): 33

[29] Taponen S, Liski E, Heikkila AM, et al. Factors associated with intramammary infection in dairy cows caused by coagulase-negative staphylococci, staphylococcus aureus, streptococcus uberis, streptococcus dysgalactiae, corynebacterium bovis, or escherichia coli [J]. Journal of dairy science, 2017, 100(1): 493-503

[30] Johnstone KJ, Robson J, Cherian SG, et al. Cystic neutrophilic granulomatous mastitis associated with corynebacterium including corynebacterium kroppenstedtii [J]. Pathology, 2017, 49(4): 405-412