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黄连素治疗慢性萎缩性胃炎的临床疗效及对患者血清 VEGF、PGⅠ、PGⅡ水平的影响 *

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摘要 目的：探讨黄连素治疗慢性萎缩性胃炎的临床疗效及对患者血清血管内皮生长因子(VEGF)、胃蛋白酶原Ⅰ(PGⅠ)、胃蛋白酶原Ⅱ(PGⅡ)水平及胃蛋白酶原Ⅰ/胃蛋白酶原Ⅱ(PGR)的影响。**方法：**选择 2015 年 1 月至 2017 年 1 月我院接诊的 96 例慢性萎缩性胃炎患者，随机分为观察组(n=48)和对照组(n=48)。对照组进行常规治疗，胃幽门螺旋杆菌(Hp)阴性的患者口服奥美拉唑肠溶胶囊，Hp 阳性的患者口服阿莫西林胶囊＋克拉霉素胶囊＋奥美拉唑肠溶胶囊，观察组联合复方黄连素片治疗。比较两组治疗前后血清 VEGF、PGⅠ、PGⅡ、PGR、Hp 阳性率的变化、临床疗效及不良反应的发生情况。**结果：**治疗后，两组血清 VEGF、PGⅠ、PGR 水平以及 Hp 阳性率均较治疗前明显改善(P＜0.05)，PGⅡ较治疗前均未有显著改变(P＞0.05)；且观察组血清 VEGF 水平、Hp 阳性率明显低于对照组(P＜0.05)，血清 PGⅠ、PGR 水平明显高于对照组(P＜0.05)；观察组临床疗效总有效率明显高于对照组(P＜0.05)。两组治疗期间均未有恶心呕吐、白细胞减少、肝肾功能异常等严重不良反应。**结论：**黄连素可显著提高慢性萎缩性胃炎患者的临床效果，其作用机制可能和改善患者血清 VEGF、PGⅠ、PGⅡ水平有关。

关键词：慢性萎缩性胃炎；黄连素；血管内皮生长因子；胃蛋白酶原

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Curative Efficacy of Berberine in the Treatment of Chronic Atrophic Gastritis and Effect on the Serum VEGF, PGⅠ, PGⅡ Levels*

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ABSTRACT Objective: To study the curative efficacy of berberine in the treatment of chronic atrophic gastritis and effect on the serum VEGF, PGⅠ, PGⅡ and PGⅠ/PGⅡ (PGR) levels. **Methods:** 96 patients of chronic atrophic gastritis who were treated from January 2015 to January 2017 in our hospital were selected and divided into the observation group (n=48) and the control group (n=48) according to random number table. The control group was treated with routine treatment, the Gastric *Helicobacter pylori* infection (Hp) negative patients were treated with oral omeprazole enteric-coated capsules, Hp positive patients were treated with oral amoxicillin capsules, clarithromycin capsules and omeprazole enteric-coated capsules, while the observation group was combined with compound berberine tablets. The changes of serum VEGF, PGⅠ, PGⅡ, PGR and Hp positive rate before and after treatment, clinical efficacy and the incidence of adverse reactions were compared between two groups. **Results:** After treatment, the serum VEGF, PGⅠ, PGR and Hp positive rate of both groups were all significantly improved compared with those before treatment (P＜0.05), there was no significant change in the serum PG II level before and after treatment in the two groups (P >0.05); the serum VEGF of observation group was significantly lower than that of the control group (P＜0.05); the serum PGⅠ, PGR of observation group were significantly higher than those of the control group(P＜0.05); the Hp positive rate of observation group were significantly lower than those of the control group(P＜0.05); the total effective rate of observation group was significantly higher than that of the control group (P＜0.05); there was no severe adverse reactions such as nau- sea, vomiting, white blood cell, and abnormal liver and kidney function in two groups. **Conclusion:** Compound berberine tablets can effectively enhance the clinical efficacy of chronic atrophic gastritis, which may be related to improvethe serum levels of VEGF, PGⅠ, PG.

Key words: Chronic atrophic gastritis; Berberine; Vascular endothelial growth factor; Pepsinogen

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前言

慢性萎缩性胃炎主要是由于胃黏膜出现萎缩性改变的慢性胃炎[1,2]，是临床常见的慢性消化系统疾病，目前已被世界卫生组织(WHO)列为胃癌的癌前状态，若未采取及时有效的治疗方案，极易进展成胃癌，对预后造成影响[3]。研究显示该病的发生、发展和较多基因的异常变化密切相关，而其中血管内皮生长因子(VEGF)的变化起着重要作用[4,5]。此外，胃蛋白酶原(PG)

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的表达也和该病的进展存在着密切关系，随着疾病进展，胃体腺萎缩、胃癌进展时，机体合成 PGⅠ、PGⅡ的功能会降低，其表达会呈明显下降趋势[6]。目前，临床上对于该病的治疗尚未有特殊疗法，多以对症治疗为主，包括杀灭胃幽门螺旋杆菌(Hp)、保护胃黏膜等。黄连素主要提取自黄连等植物，近年来研究表明证实其在杀菌消炎、调节免疫、抗肿瘤中均可达到满意的成效[7,8]。本研究旨在探讨复方黄连素片治疗慢性萎缩性胃炎患者的临床疗效其对血清 VEGF、PGⅠ、PGⅡ水平的影响，现报道如下。

1 资料与方法

1.1 一般资料

选择 2015 年 1 月至 2017 年 1 月我院接诊的 96 例慢性萎缩性胃炎患者。纳入标准[9]：① 符合慢性萎缩性胃炎诊断标准；② 年龄 18~70 岁；③ 知情同意此研究。排除标准[10]：① 十二指肠溃疡、胃溃疡、胃癌；② 伴有恶性肿瘤、血液疾病等；③ 肝、肾、心功能等障碍；④ 妊娠期；⑤ 对研究药物过敏。以随机数表法将所有患者分为 2 组，每组各 48 例。观察组男 27 例，女 21 例；年龄 26~69 岁，平均(47.83± 4.57)岁；病程 1~17 年，平均(8.23± 1.56)年。对照组男 25 例，女 23 例；年龄 24~68 岁，平均(48.01± 4.49)岁；病程 1~19 年，平均(8.29± 1.50)年。两组一般资料比较差异无统计学意义(P＞0.05)，具有可比性。

1.2 治疗方法

对所有受试者进行 C14 呼吸试验，判断 Hp 阳性或阴性。对照组：Hp 阴性患者口服奥美拉唑肠溶胶囊 (规格 20 mg，厂家：浙江京新药业股份有限公司，国药准字 H20065588)，剂量 20 mg，2 次 /d；Hp 阳性患者口服阿莫西林胶囊(规格 0.25 g，厂家：广州白云山制药股份有限公司，国药准字 H44021518)，剂量 1 g，克拉霉素胶囊(规格 0.25 g，厂家：江苏福邦药业有限公司，国药准字 H20083442)，剂量 0.5 mg，奥美拉唑肠溶胶囊，剂量 20 mg，2 次 /d。观察组：联用复方黄连素片(规格 30mg，厂家：湖北诺得胜制药有限公司，国药准字 Z42020259)的口服，剂量 60 mg，2 次 /d。两组均以 7d 为 1 疗程，连续治疗 2 个疗程。

1.3 观察指标

1.3.1 **血清因子** 抽取 5 mL 空腹静脉血，以酶联免疫吸附法对 VEGF、PGⅠ、PGⅡ的表达进行检测，选择美国佰腾生产的 Elx808 全自动酶标仪，试剂盒均购于深圳晶美生物技术有限公司；PCR= PGⅠ / PGⅡ。

1.3.2 **Hp 阳性率** 行 C14 呼吸试验，记录阳性表达率。

1.3.3 **不良反应** 包括恶心呕吐、白细胞减少、肝功损伤等。

1.4 疗效评定标准

显效：Hp 检测结果阴性，上腹疼痛、反酸等症状消失，患者主诉已无不适感，通过胃镜检查显示胃黏膜充血、糜烂、水肿情况消失；有效：Hp 检测结果为弱阳性或阴性；上腹痛、反酸等症状仍偶尔出现，但较治疗前明显缓解，通过胃镜检查结果显示胃黏膜充血、糜烂、水肿情况得到缩小，部分粘膜已有所愈合；无效：Hp 为阳性，上腹痛、反酸等症状无明显缓解，甚至加剧，胃镜检查结果也无明显改善。以显效 + 有效为总有效率。

1.5 统计学分析

数据用 SPSS 18.0 软件包处理，计量资料用均数± 标准差($\bar{x}$± s)表示，并采用 t 检验，计数资料的比较采用 x^2 检验，P<0.05 表示差异具有统计学意义。

2 结果

2.1 两组治疗前后血清 VEGF 水平的比较

治疗前，两组血清 VEGF 水平比较差异无统计学意义(P＞0.05)；治疗后，两组血清 VEGF 水平较治疗前均显著降低(P＜0.05)，且观察组血清 VEGF 水平明显低于对照组(P＜0.05)，见表 1。

表 1 两组治疗前后血清 VEGF 水平的比较($\bar{x}$± s，pg/mL)

Table 1 Comparison of the serum VEGF level before and after treatment between two groups($\bar{x}$± s, pg/mL)

Groups		VEGF
Observation group(n=48)	Before treatment	73.42± 12.86
	After treatment	33.75± 7.34*#
Control group(n=48)	Before treatment	73.60± 12.81
	After treatment	51.23± 9.34*

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

2.2 两组治疗前后血清 PGⅠ、PGⅡ水平的比较

治疗前，两组血清 PGⅠ、PGⅡ及 PGR 比较差异均无统计学意义(P＞0.05)；治疗后，两组血清 PGⅠ水平、PGR 均较治疗前显著改善(P＜0.05)，观察组血清 PGⅠ水平、PGR 均明显高于对照组 (P＜0.05)，两组治疗前后血清 PGⅡ均未有显著改变(P＞0.05)，见表 2。

表 2 两组治疗前后血清 PGⅠ、PGⅡ水平及 PGR 比较($\bar{x}$± s)

Table 2 Comparison of the serum PGⅠ, PGⅡ levels and PGR before and after treatment between two groups ($\bar{x}$± s)

Groups		PGⅠ(μg/L)	PGⅡ(μg/L)	PCR
Observation group(n=)	Before treatment	74.53± 13.04	4.53± 0.82	17.84± 1.25
	After treatment	131.72± 16.73*#	4.67± 0.81	25.68± 1.72*#
Control group(n=)	Before treatment	74.81± 12.76	4.50± 0.83	17.76± 1.28
	After treatment	105.64± 13.46*	4.69± 0.79	21.04± 1.35*

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

2.3 两组治疗前后 Hp 阳性率比较

治疗前，两组 Hp 阳性率比较差异无统计学意义(P＞0.05)；治疗后，两组 Hp 阳性率均较治疗前显著降低(P＜0.05)，观察组 Hp 阳性率明显低于对照组(P＜0.05)，见表 3。

表 3 两组治疗前后 Hp 阳性率的比较(例，%)

Table 3 Comparison of the Hp positive rate before and after treatment between two groups (n, %)

Groups		Hp positive rate
Observation group(n=48)	Before treatment	35(72.92)
	After treatment	9(18.75)*#
Control group(n=48)	Before treatment	36(75.00)
	After treatment	17(35.42)*

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

2.4 两组临床疗效比较

观察组总有效率为 93.75%，明显比对照组高(66.67%，P＜0.05)，见表 4。

表 4 两组临床疗效的比较(例，%)

Table 4 Comparison of the clinical efficacy between two groups (n, %)

Groups	Effective	Valid	Invalid	Total effective rate
Observation group(n=48)	28(58.33)	17(35.42)	3(6.25)	45(93.75)*
Control group(n=48)	19(39.58)	13(27.08)	16(33.33)	32(66.67)

Note: Compared with the control group, *P＜0.05.

2.5 两组不良反应发生情况的比较

两组治疗期间均未有恶心呕吐、白细胞减少、肝肾功能异常等严重不良反应。

3 讨论

慢性萎缩性胃炎是临床上较为常见的消化系统疾病，也是胃癌的癌前状态，目前该病已受到诸多临床学者关注，对于该病的发病机制目前仍未有确切论证，多数学者认为其和碱液反流、胃动力障碍、Hp 感染存在着密切关系，其中 Hp 感染是公认的病因，在 Hp 感染后，可使粘膜发生免疫反应，刺激多种细胞因子继发，通过细胞因子发挥持续作用，致使感染慢性化，继而使慢性炎症逐渐成功肿瘤[11,12]。且 HP 感染作为胃黏膜炎症反应的始动因素，炎症反应的失衡可引发黏膜损伤、炎症慢性化，严重的甚至出现全身症状。相关研究指出，对于该病的治疗关键是根除 Hp 感染，但目前临床上所采用的对症治疗措施仍得不到令人满意的效果[13]。

黄连素是种异喹啉类生物碱，主要提取于黄连等植物中，既往临床上多用于解毒清热、肠道感染等的治疗，随着学者们的不断研究，近年来国内外均研究证实其具有杀菌消炎、调节免疫、抗肿瘤等效果[14,15]。我国 Jiang JF 等[16]报道称黄连素可令葡聚糖硫酸钠所诱导的胃肠道损伤及炎症程度明显改善，且其还可对上皮细胞、巨噬细胞中的促炎因子产生抑制作用，令肿瘤坏死因子、白介素(IL)-17 等炎症因子水平降低，继而促进胃肠道巨噬细胞凋亡。国外 Mittal J 等[17]研究证实黄连素抗菌谱广，可抑制 Hp 的增殖和 N- 乙酰基转移酶的活性，并同时令 Hp 感染对细胞的毒性作用降低。本研究结果显示联用复方黄连素片治疗的患者 Hp 阳性率明显降低，临床疗效高达 93.75%，明显比常规治疗患者的 66.67%更具有优势，提示复方黄连素片抑菌、杀菌效果显著，和既往国内外学者研究具有相似性。Zhaojie M 等[18]的研究也显示复方黄连素片可直接在平滑肌产生作用，有效接触痉挛，起到缓解腹痛等作用，有助于改善临床症状，提高临床疗效。此外，患者均未有不良反应发生，通过分析是由于黄连素不会被吸收入血，只在消化道停留，安全性较高，和 Xie D 等[19]研究具有相似性。

VEGF 又被称作是血管通透因子，可通过特殊的受体对磷脂酶产生激活作用，快速诱导钙离子直接作用于血管内皮细胞，令微血管通透性增加，其在垂体、肾上腺、肾脏、脑、卵巢等各组织中均有所分布[20]。相关研究表明 VEGF 在肿瘤生长过程中的血管形成中发挥着重要作用，其不仅可为肿瘤的生长提供营养物质，且可排除代谢产物，促使血管渗漏，还是癌细胞转移扩散的重要途径[21]。近年来，国内外均有学者证实 VEGF 和胃癌的发生具有密切关系，在胃癌早期即有 VEGF 的分泌[22,23]。Huang J 等[24]对慢性萎缩性胃炎和胃癌患者的各阶段 VEGF 的分析结果显示随着疾病的加重，其表达呈明显升高趋势，并提出检测 VEGF 有助于了解疾病严重程度。在本研究中，联用复方黄连素片的患者 VEGF 的下降程度明显优于常规治疗患者，可能与黄连素具有抗肿瘤活性，可诱导细胞凋亡、抑制血管生成等作用相关[25]。Pan Y 等[26]的研究也证实，黄连素的确可抑制胃癌细胞增值。

随着慢性萎缩性胃炎的不断进展，胃黏膜中的腺体的分泌功能也逐渐衰退，PG 作为胃黏膜细胞所分泌的重要蛋白酶前提，主要包括 PGⅠ、PGⅡ2 个亚群[27]。PG 会在胃中蛋白酶或盐酸的作用下，转化为具有活性的胃蛋白酶，而当胃黏膜萎缩时，所分泌的蛋白酶腺体会降低，或被幽门腺体所代替 PGⅠ的表达则会呈降低状态。PGⅡ所分泌的腺体较广，胃黏膜萎缩时不会对其造成较大的影响，因此 PGR 比值会呈降低表达；且通过

对PGⅠ、PGⅡ的干预，可促进胃黏膜腺体功能的改善[28,29]，本研究结果显示，联合复方黄连素片治疗的患者PGⅠ、PGR明显增加，效果优于常规治疗的患者，显示出复方黄连素片可明显干预PG的表达。Wang J等[30]试验也显示黄连素可促进胃泌素生成，对萎缩粘膜的生长具有刺激作用，有助于改善胃黏膜腺体功能。这也可能是应用该方式的患者临床疗效更为显著的内在机制之一。

综上所述，在慢性萎缩性胃炎患者中应用黄连素治疗效果显著，可有效缓解临床症状，且用药安全性高，其作用机制可能和改善VEGF、PGⅠ、PGⅡ、PGR的表达相关。

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