

doi: 10.13241/j.cnki.pmb.2018.15.019

生血宁片联合琥珀酸亚铁片治疗妊娠期缺铁性贫血患者的疗效 及对铁代谢的影响 *

阮晟鸣 吴芝萍 王惠敏 周 健 单震丽

(上海市第一妇婴保健院妇产科 上海 201204)

摘要 目的: 探讨生血宁片联合琥珀酸亚铁片治疗妊娠期缺铁性贫血患者的疗效及对铁代谢的影响。**方法:** 选取 2015 年 2 月-2017 年 2 月我院收治的妊娠期缺铁性贫血患者 200 例为研究对象。将其以随机数字表法分成对照组($n=100$)和研究组($n=100$)。对照组予以口服琥珀酸亚铁片治疗,研究组则予以生血宁片联合琥珀酸亚铁片治疗,两组均连续治疗 4 周。分别比较两组临床疗效、治疗前后血液学指标、治疗前后铁代谢指标以及不良妊娠结局情况。**结果:** 研究组治疗总有效率明显较对照组升高($P<0.05$)。治疗后两组患者血红蛋白(Hb)、红细胞(RBC)、平均红细胞体积(MCV)以及平均红细胞血红蛋白浓度(MCHC)水平均明显高于治疗前,且研究组高于对照组($P<0.05$)。治疗后两组患者血清铁、转铁蛋白饱和度(TSAT)水平均明显高于治疗前,且研究组又明显高于对照组($P<0.05$)。与对照组比较,研究组不良妊娠结局发生率降低($P<0.05$)。**结论:** 生血宁片联合琥珀酸亚铁片治疗妊娠期缺铁性贫血患者的临床疗效显著,改善患者血液学指标以及铁代谢水平,降低不良妊娠结局发生风险,值得临床推广应用。

关键词: 妊娠期缺铁性贫血;生血宁片;琥珀酸亚铁片;铁代谢;不良妊娠结局

中图分类号: R714.254 **文献标识码:** A **文章编号:** 1673-6273(2018)15-2894-04

Curative Effect of Shengxuening Tablets Combined with Ferrous Succinate Tablets on Patients with Iron Deficiency Anemia During Pregnancy*

RUAN Sheng-ming, WU Zhi-ping, WANG Hui-min, ZHOU Jian, SHAN Zhen-li

(Department of Gynaecology and Obstetrics, Shanghai First Maternity and Infant Hospital, Shanghai, 201204, China)

ABSTRACT Objective: To investigate the curative effect of Shengxuening tablets combined with ferrous succinate tablets in the treatment of patients with iron deficiency anemia during pregnancy and its effect on iron metabolism. **Methods:** A total of 200 patients with iron deficiency anemia during pregnancy, who were treated in Shanghai First Maternity and Infant Hospital from February 2015 to February 2017, were selected and randomly divided into control group ($n=100$) and study group ($n=100$). The control group was treated with oral Ferrous Succinate Tablets, and the study group was treated with Shengxuening tablets combined with ferrous succinate tablets. The two groups were treated continuously for 4 weeks. The clinical efficacy, the hematology indexes before and after treatment, the iron metabolism indexes before and after treatment, and the adverse pregnancy outcome were compared between the two groups. **Results:** The total effective rate of treatment in the study group was significantly higher than that in the control group ($P<0.05$). After treatment, the levels of hemoglobin (Hb), red blood cell (RBC), mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) of the two groups were significantly higher than those before treatment, and the study group was higher than that in the control group ($P<0.05$). After treatment, the levels of serum iron and transferrin saturation (TSAT) in the two groups were significantly higher than those before treatment, and the study group was significantly higher than that of the control group ($P<0.05$). Compared with the control group, the incidence of adverse pregnancy outcomes in the study group was reduced ($P<0.05$). **Conclusion:** Shengxuening tablets combined with Ferrous Succinate Tablets has a significant curative effect in the treatment of patients with iron deficiency anemia during pregnancy, and it can improve the hematological indexes and iron metabolism of patients and reduce the risk of adverse pregnancy outcomes, which is worthy of clinical application.

Key words: Iron deficiency anemia during pregnancy; Shengxuening tablets; Ferrous Succinate Tablets; Iron metabolism; Adverse pregnancy outcome

Chinese Library Classification(CLC): R714.254 **Document code:** A

Article ID: 1673-6273(2018)15-2894-04

前言

贫血属于妊娠过程中较为多见的一种代谢失衡类疾病,且大部分患者为妊娠期缺铁性贫血^[1,2]。该病患者主要临床症状包

* 基金项目:上海市科学技术委员会科研基金项目(12DZ2260915)

作者简介:阮晟鸣(1978-),女,本科,主治医师,从事妇产科方面的研究,E-mail:awsgow@163.com

(收稿日期:2018-01-17 接受日期:2018-02-13)

括疲惫无力、黏膜以及皮肤血行不畅等,病情严重者甚至会出现神经系统以及消化系统异常等症状,对患者的生命健康安全造成了一定威胁^[3-5]。另有研究报道显示,妊娠期缺铁性贫血会导致孕妇供给胎儿的营养物质显著减少,进一步对胎儿的正常生长发育产生不利影响,增加了一系列不良妊娠结局发生的风险^[6-8]。因此,早期明确诊断妊娠期缺铁性贫血,并予以及时有效的补铁措施以及营养干预计划显得尤为重要。目前,临床上主要采用琥珀酸亚铁治疗妊娠期缺铁性贫血,该治疗方式可显著改善贫血症状,但单纯使用具有一定的局限性^[9,10]。而生血宁片可通过改善患者铁代谢情况,从而促进造血功能的恢复,以达到改善贫血的目的^[11]。鉴于此,本文通过探讨生血宁片联合琥珀酸亚铁片治疗妊娠期缺铁性贫血患者的疗效及对铁代谢的影响,旨在为临床有效治疗妊娠期缺铁性贫血提供一种有效治疗方法。现作以下阐述。

1 资料与方法

1.1 一般资料

将我院在 2015 年 2 月-2017 年 2 月收治的 200 例妊娠期缺铁性贫血患者作为研究对象。纳入标准^[12]:(1)所有患者均符合《血液病诊断及疗效标准》中妊娠期缺铁性贫血的诊断标准;(2)均为单胎妊娠;(3)年龄>20 岁;(4)均为初发妊娠期缺铁性贫血;(5)患者及其家属均签署了知情同意书。排除标准:(1)伴有妊娠期高危并发症者;(2)入院前接受过补铁制剂治疗者;(3)合并心、肝、肾等脏器功能严重障碍者;(4)存在代谢系统疾病者;(5)临床病历资料缺失者。将所有患者以随机数字表法均分成对照组(n=100)和研究组(n=100)。其中研究组年龄 22-36 岁,平均年龄(26.52±2.74)岁;孕周 23-39 周,平均孕周(32.41±2.61)周。对照组年龄 21-38 岁,平均年龄(26.14±2.76)岁;孕周 21-35 周,平均孕周(31.86±2.17)周。两组患者年龄及孕周比较,差异无统计学意义(P>0.05),均衡可比。我院伦理委员会已批准同意。

1.2 研究方法

所有患者入院后均予以营养、饮食指导,叮嘱患者多摄入

富含铁的食物。对照组口服琥珀酸亚铁片(四川奥邦药业有限公司,国药准字:H20083003,规格:0.1 g)治疗,2 片/次,3 次/d。研究组则在对照组的基础上予以生血宁片(武汉联合药业有限责任公司,国药准字:Z20030088,规格:0.25 g)治疗,2 片/次,3 次/d。两组均连续治疗 28 天。

1.3 观察指标

分别比较两组治疗前后血液学指标、治疗前后铁代谢指标以及不良妊娠结局情况以及临床疗效。治疗前及治疗 28 天后分别抽取两组患者的晨间空腹静脉血约 4 mL,给予 10 min 3000 r/min 的离心后提取血清。采用血细胞分析仪法测定患者血液学指标水平,主要包括血红蛋白(hemoglobin, Hb)、红细胞(red blood cell, RBC)、平均红细胞体积(mean corpuscular volume, MCV)以及平均红细胞血红蛋白浓度(mean erythrocyte hemoglobin concentration, MCHC)。治疗前后分别采用全自动分析仪测定血清铁水平,采用铁蛋白免疫电泳实验测定转铁蛋白饱和度(transferin saturation, TSAT)水平。不良妊娠结局包括早产、新生儿窒息、低出生体重等。

1.4 疗效评价

疗效判定标准如下^[13]:(1)治愈:治疗 28 天后血清铁与 Hb 恢复至正常水平,且患者临床症状完全消失;(2)显效:治疗 28 天后血清铁与 Hb 基本改善,患者临床症状有所缓解;(3)有效:治疗 28 天后血清铁与 Hb 有所改善,患者临床症状减轻;(4)无效:治疗 28 天后患者血清铁及 Hb、临床症状均无改善。总有效率为治愈率、显效率、有效率之和。

1.5 统计学方法

数据统计分析采用 SPSS20.0 软件进行,血液学指标水平、铁代谢指标水平等计量资料以($\bar{x} \pm s$)表示,实施 t 检验,有效率、不良妊娠结局情况等计数资料以[n(%)]表示,实施 χ^2 检验,检验水准设置为 $\alpha=0.05$ 。

2 结果

2.1 两组疗效对比

研究组治疗总有效率较对照组升高(P<0.05)。见表 1。

表 1 两组疗效对比[n(%)]

Table 1 Comparison of curative effect between two groups[n(%)]

Groups	n	Cure	Excellence	Effective	Invalid	Total effective rate
Study group	100	22(22.00)	28(28.00)	39(39.00)	11(11.00)	89(89.00)
Control group	100	19(19.00)	24(24.00)	34(34.00)	23(23.00)	77(77.00)
χ^2	-					5.103
P	-					0.024

2.2 两组患者血液学指标水平对比

两组患者治疗前各项血液学指标水平对比无明显差异(P>0.05),而治疗后两组患者 Hb、RBC、MCV、MCHC 水平均明显高于治疗前,且研究组高于对照组(P<0.05)。见表 2。

2.3 两组铁代谢指标水平对比

两组患者治疗前血清铁、TSAT 水平对比无明显差异(P>0.05),而治疗后两组患者血清铁、TSAT 水平均明显高于治疗前,且研究组又明显高于对照组(P<0.05)。见表 3。

2.4 两组不良妊娠结局情况对比

研究组不良妊娠结局发生率较对照组降低(P<0.05)。见表 4。

3 讨论

缺铁性贫血属于妊娠期妇女较为常见的一种贫血,在所有妊娠期贫血中约占 95%^[14-16]。其中导致该病发生的主要原因在于铁的需求量显著增加,而孕妇体内的铁量缺乏,加之食物中摄入的铁量不足。孕妇一旦发生缺铁性贫血,会对孕妇及胎儿

表 2 治疗前后两组患者各项血液学指标水平对比($\bar{x} \pm s$)

Table 2 Comparison of the levels of Haematological index of two groups before and after treatment($\bar{x} \pm s$)

Groups	Time	Hb (mg/ml)	RBC($\times 10^{12}/L$)	MCV (fL)	MCHC (%)
Study group(n=100)	Before treatment	83.22 $\pm$ 9.78	2.30 $\pm$ 0.53	60.22 $\pm$ 13.36	17.79 $\pm$ 2.98
	After treatment	137.38 $\pm$ 18.09 [#]	5.18 $\pm$ 0.67 [#]	91.57 $\pm$ 14.18 [#]	29.81 $\pm$ 3.65 [#]
Control group(n=100)	Before treatment	85.92 $\pm$ 10.56	2.24 $\pm$ 0.59	60.41 $\pm$ 13.34	18.26 $\pm$ 2.86
	After treatment	115.66 $\pm$ 16.82 [#]	2.93 $\pm$ 0.62 [#]	85.11 $\pm$ 14.05 [#]	25.12 $\pm$ 3.27 [#]

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

表 3 治疗前后两组铁代谢指标水平对比($\bar{x} \pm s$)

Table 3 Comparison of iron metabolism indexes before and after treatment($\bar{x} \pm s$)

Groups	n	Serum iron(μ mol/L)		TSAT(%)	
		Before treatment	After treatment	Before treatment	After treatment
Study group	100	4.87 $\pm$ 1.15	22.25 $\pm$ 2.96 [#]	19.24 $\pm$ 3.15 [#]	32.72 $\pm$ 5.11 [#]
Control group	100	5.02 $\pm$ 1.28	14.51 $\pm$ 2.52 [#]	19.95 $\pm$ 3.26 [#]	23.15 $\pm$ 4.05 [#]
t	-	0.872	19.910	1.566	14.677
P	-	0.384	0.000	0.119	0.000

Note: compared with before treatment, [#]P<0.05.

表 4 两组不良妊娠结局情况对比[n(%)]

Table 4 Comparison of adverse pregnancy outcomes between two groups[n(%)]

Groups	n	Premature birth	Asphyxia neonatorum	Low birth weight	Incidence of bad pregnancy
Study group	100	1(1.00)	1(1.00)	0(0.00)	2(2.00)
Control group	100	3(3.00)	3(3.00)	3(3.00)	9(9.00)
χ^2					4.714
P					0.030

带来不同程度的影响,病情严重时甚至会导致孕产妇或围生儿死亡^[17-19]。目前,临床上治疗妊娠期缺铁性贫血的原则主要包括消除导致缺铁性贫血的相关因素,同时予以患者补充有效的铁剂。琥珀酸亚铁片属于临床上广泛应用于妊娠期缺铁性贫血的传统药物,属于非处方矿物质类药物^[20,21]。然而,该药物虽然具有一定的疗效,但易导致患者发生一系列不良反应,存在一定的局限性。且有研究报道表明,采用琥珀酸亚铁片治疗时需定期检查患者的血铁水平以及血象,从而达到防治过度治疗的目的,存在一定的局限性^[22]。因此,寻找一种更加安全、有效的治疗方式显得尤为重要,其对改善患者临床症状,避免不良妊娠结局的发生具有极其重要的意义。

本研究结果显示:研究组治疗总有效率较对照组升高(P<0.05),这与刘丽恒等人的研究报道相一致^[23],说明了生血宁片与琥珀酸亚铁片联合治疗妊娠期缺铁性贫血具有显著的临床疗效。分析原因,可能与生血宁片的药理作用有关。具体而言,生血宁片主要成分包括蚕砂,其味属辛甘、性较温和,可入肝脾经,具有益气、补血、止血以及滋阴润燥的作用,应用于缺铁性贫血患者中具有显著效果,从而可提高临床治疗效果^[24,25]。此外,治疗后研究组 Hb、RBC、MCV、MCHC 水平均明显高于对照组(P<0.05),这表明了生血宁片与琥珀酸亚铁片联合治疗妊娠期缺铁性贫血可有效改善患者血液学指标。分析其主要原因在于生血宁片具有补充铁元素的作用,同时可促进骨髓发挥造血功能,进一步达到改善贫血症状,促进血液学指标的恢复。

另外,治疗后研究组血清铁、TSAT 水平均明显高于对照组(P<0.05),这提示了生血宁片与琥珀酸亚铁片联合治疗妊娠期缺铁性贫血可显著改善患者铁代谢指标。究其原因,可能是生血宁片中的蚕砂中含有一定量的铁叶绿酸钠,其属于天然卟啉类化合物,亦是治疗缺铁性贫血的第三代药物,患者口服后可直接被肠道黏膜细胞所吸收,且吸收率相较硫酸亚铁吸收率高 12.5 倍,具有极少的不良反应^[26,27]。本研究结果还发现,研究组不良妊娠结局发生率低于对照组(P<0.05),这也再次证实了生血宁片与琥珀酸亚铁片联合治疗妊娠期缺铁性贫血可有效降低患者不良妊娠结局发生率。分析原因可能与生血宁片造成的胃肠道不良反应较少有关^[28]。

综上所述,生血宁片联合琥珀酸亚铁片治疗妊娠期缺铁性贫血患者具有明显的临床疗效,同时有利于改善患者血液学指标以及铁代谢,降低不良妊娠结局发生率,可作为临床上治疗妊娠期缺铁性贫血的首选方案。

参考文献(References)

- Engwa GA, Unaegbu M, Unachukwu MN, et al. Low serum ferritin and G6PD deficiency as potential predictors of anaemia in pregnant women visiting Prime Care Hospital Enugu Nigeria [J]. BMC Res Notes, 2017, 10(1): 721
- Sholeye OO, Animasahun VJ, Shorunmu TO. Anemia in pregnancy and its associated factors among primary care clients in Sagamu, Southwest, Nigeria: A facility-based study [J]. J Family Med Prim Care, 2017, 6(2): 323-329

- [3] Öztürk M, Öztürk Ö, Ulubay M, et al. Anemia prevalence at the time of pregnancy detection. *Anemia prevalence at the time of pregnancy detection*[J]. *Turk J Obstet Gynecol*, 2017, 14(3): 176-180
- [4] Senadheera D, Goonewardene M, Mampitiya I. Anaemia and iron deficiency in pregnant women attending an antenatal clinic in a Teaching Hospital in Southern Sri Lanka[J]. *Ceylon Med J*, 2017, 62(3): 175-183
- [5] Mishra V, Gandhi K, Roy P, et al. Role of Intravenous Ferric Carboxy-maltose in Pregnant Women with Iron Deficiency Anaemia[J]. *J Nepal Health Res Counc*, 2017, 15(2): 96-99
- [6] Smith LE, Prendergast AJ, Turner PC, et al. Aflatoxin Exposure During Pregnancy, Maternal Anemia, and Adverse Birth Outcomes[J]. *Am J Trop Med Hyg*, 2017, 96(4): 770-776
- [7] Kawasaki K, Kondoh E, Minamiguchi S, et al. Live-born diploid fetus complicated with partial molar pregnancy presenting with pre-eclampsia, maternal anemia, and seemingly huge placenta: A rare case of confined placental mosaicism and literature review [J]. *J Obstet Gynaecol Res*, 2016, 42(8): 911-917
- [8] Breymann C, Honegger C, Hösli I, et al. Diagnosis and treatment of iron-deficiency anaemia in pregnancy and postpartum [J]. *Arch Gynecol Obstet*, 2017, 296(6): 1229-1234
- [9] 徐谟燕,柴竟竞.琥珀酸亚铁片对妊娠合并缺铁性贫血的疗效及血红蛋白、红细胞、血清铁蛋白的影响[J].*实用药物与临床*, 2014, 17(5): 634-635, 636
Xu Mo-yan, Chai Jing-jing. Efficacy of ferrous succinate tablets on iron deficiency anemia during pregnancy and impact on hemoglobin, red blood cells, serum ferritin [J]. *Practical Pharmacy and Clinical Remedies*, 2014, 17(5): 634-635, 636
- [10] Berglund SK, Lindberg J, Westrup B, et al. Effects of iron supplements and perinatal factors on fetal hemoglobin disappearance in LBW infants[J]. *Pediatr Res*, 2014, 76(5): 477-482
- [11] Cheng X, Yu G, Hu J, et al. Clinical study of Shengxuening tablet combined with rHuEPO for the treatment of renal anemia of maintenance hemodialysis patients[J]. *Exp Ther Med*, 2016, 12(1): 157-160
- [12] 邓念英,陈海燕,罗培英,等.蛋白琥珀酸铁治疗妊娠期缺铁性贫血疗效观察[J].*中国药师*, 2015, 18(9): 1546-1548
Deng Nian-ying, Chen Hai-yan, Luo Pei-ying, et al. Efficacy of Iron Protein Succinylate in the Treatment of Iron-deficiency Anemia during Pregnancy[J]. *China Pharmacist*, 2015, 18(9): 1546-1548
- [13] 张飞虹,胡君华.琥珀酸亚铁治疗妊娠合并缺铁性贫血的疗效与安全性观察[J].*中国药房*, 2015, 26(24): 3335-3336
Zhang Fei-hong, Hu Jun-hua. Efficacy and Safety Observation of Ferrous Succinate in the Treatment of Pregnancy Complicated with Iron Deficiency Anemia[J]. *China Pharmacy*, 2015, 26(24): 3335-3336
- [14] Habib MA, Raynes-Greenow C, Soofi SB, et al. Prevalence and determinants of iron deficiency anemia among non-pregnant women of reproductive age in Pakistan [J]. *Asia Pac J Clin Nutr*, 2018, 27(1): 195-203
- [15] Breymann C, Auerbach M. Iron deficiency in gynecology and obstetrics: clinical implications and management [J]. *Hematology Am Soc Hematol Educ Program*, 2017, 2017(1): 152-159
- [16] PLOS ONE Staff. Correction:Iron deficiency was not the major cause of anemia in rural women of reproductive age in Sidama zone, southern Ethiopia: A cross-sectional study [J]. *PLoS One*, 2017, 12(12): e0189553
- [17] Naqash A, Ara R, Bader GN. Effectiveness and safety of ferric carboxymaltose compared to iron sucrose in women with iron deficiency anemia: phase IV clinical trials [J]. *BMC Womens Health*, 2018, 18(1): 6
- [18] Yung DE, Rondonotti E, Giannakou A, et al. Capsule endoscopy in young patients with iron deficiency anaemia and negative bidirectional gastrointestinal endoscopy[J]. *United European Gastroenterol J*, 2017, 5(7): 974-981
- [19] Joshi K, Nair S, Khade C, et al. Early gestation screening of pregnant women for iodine deficiency disorders and iron deficiency in urban centre in Vadodara, Gujarat, India [J]. *J Dev Orig Health Dis*, 2014, 5(1): 63-68
- [20] 何玲玲,黄粤,朱津,等.琥珀酸亚铁叶酸片干预对孕晚期贫血孕妇母婴结局的影响[J].*哈尔滨医药*, 2017, 37(2): 158-159
He Ling-ling, Huang Yue, Zhu Jin, et al. Effect of ferrous succinate Folic Acid Tablets intervention on maternal and child outcome of pregnant women with anemia in the late pregnancy [J]. *Harbin Medical Journal*, 2017, 37(2): 158-159
- [21] Dvoretzky LI. Ferrous sulfate in the treatment of iron deficiency anemia: The positions continue[J]. *Ter Arkh*, 2017, 89(10): 108-112
- [22] 王浩. 琥珀酸亚铁联合复方红衣补血口服液预防妊娠期贫血的临床研究[J].*河北医药*, 2014, 39(17): 2596-2597
Wang Hao. Clinical study on the prevention of anemia in pregnancy by the combination of ferrous succinate and red coat blood tonifying oral liquid[J]. *Hebei Medical Journal*, 2014, 39(17): 2596-2597
- [23] 刘丽恒,王小新,王欣,等.生血宁治疗妊娠期缺铁性贫血的临床研究[J].*中国临床医生杂志*, 2016, 44(6): 90-92
Liu Li-heng, Wang Xiao-xin, Wang Xin, et al. Clinical study on Shengxuening in treatment of iron deficiency anemia in pregnancy period[J]. *Chinese Journal for Clinicians*, 2016, 44(6): 90-92
- [24] Chen HQ, Zou SH, Yang JB, et al. A survey and analysis of using traditional Chinese medicine during pregnancy [J]. *Int J Clin Exp Med*, 2015, 8(10): 19496-19500
- [25] 彭丹丽. 生血宝合剂联合生血宁片治疗妊娠期缺铁性贫血的疗效观察[J].*现代药物与临床*, 2017, 32(5): 856-859
Peng Zhou-li. Clinical observation of Shengxuebao Mistura combined with Shengxuening Tablets in treatment of iron deficiency anemia in pregnancy[J]. *Drugs & Clinic*, 2017, 32(5): 856-859
- [26] 黄飞鸿,朱林杰,李迪迪,等.生血宁片对环磷酰胺致贫血小鼠的作用及机制[J].*中成药*, 2016, 38(6): 1205-1210
Huang Fei-hong, Zhu Lin-jie, Li Di-di, et al. Effect of Shengxuening Tablets on mice with cyclophosphamide-induced anemia and its mechanism [J]. *Chinese Traditional Patent Medicine*, 2016, 38(6): 1205-1210
- [27] 杨卫东. 生血宁片治疗围生期孕妇贫血疗效和不良反应发生情况研究[J].*首都食品与医药*, 2017, 24(20): 86-87
Yang Wei-dong. Clinical research of curative effect and adverse reaction incidence of Shengxuening tablets in the treatment of anemia in pregnant women during perinatal stage[J]. *Capital Medicine*, 2017, 24(20): 86-87
- [28] 张瑞杰. 孕中期常规口服生血宁片预防孕妇缺铁性贫血的疗效观察[J].*河北医药*, 2014, 39(16): 2464-2466
Zhang Rui-jie. The curative effect of second trimester routine oral Shengxuening tablet in the prevention of iron deficiency anemia in pregnant women[J]. *Hebei Medical Journal*, 2014, 39(16): 2464-2466