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罗沙司他治疗肾性贫血的效果观察及对 TSAT、Cys C 及 NOX2 的作用分析 *

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摘要 目的：探讨罗沙司他治疗肾性贫血的效果观察及对转铁蛋白饱和度（TSAT）、胱抑素 C（Cys C）及 NADPH 氧化酶 2（NOX2）的作用。**方法**：选择 2019 年 12 月到 2020 年 12 月在我院接受治疗的 125 例肾性贫血患者，采用随机数表法分为试验组（n=63）和对照组（n=62）。对照组给予重组人促红素治疗，试验组给予罗沙司他治疗。比较两组临床疗效、TSAT、Cys C、NOX2、红细胞计数（RBC）、血红蛋白（Hb）、血细胞比容（Hct）、铁蛋白（SF）、转铁蛋白（TRF）及铁调素（Hepc）水平变化情况及药物不良反应发生情况。**结果**：治疗后，两组总有效率比较差异显著（P<0.05）；治疗前，试验组和对照组血清 TSAT、Cys C 及 NOX2 比较无显著差异；治疗后，试验组和对照组血清 TSAT 随着时间的推移而升高，且试验组高于对照组，Cys C 及 NOX2 随着时间的推移而升减降低，且试验组低于对照组，差异显著（P<0.05）；治疗前，试验组和对照组 RBC、Hb、Hct 检验结果比较无显著差异；治疗后，试验组和对照组 RBC、Hb、Hct 均随着时间的推移而升高，且试验组高于对照组，差异显著（P<0.05）；治疗前，试验组和对照组 SF、TRF 及 Hepc 检验结果比较无显著差异；治疗后，试验组和对照组血清 SF、TRF 均随着时间的推移而升高，且试验组高于对照组，Hepc 随着时间的推移而下降，且试验组低于对照组，差异显著（P<0.05）；两组不良反应总发生率分别为 4.76%、8.06%（P>0.05）。**结论**：在肾性贫血患者中应用罗沙司他效果显著，可能与其可有效改善血清 TSAT、Cys C 及 NOX2 水平有关，且不增加不良反应。

关键词：罗沙司他；肾性贫血；转铁蛋白饱和度；胱抑素；NADPH 氧化酶 2

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Curative Efficacy of Observation on the Effect of Roxathat on Renal Anemia and Its Effect on TSAT, Cys C and NOX2*

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ABSTRACT Objective: To study Curative efficacy of Observation on the effect of roxathat on renal anemia and its effect on Transferrin saturation (TSAT), cystatin C (Cys C) and NADPH oxidase 2 (NOX2). **Methods:** 125 patients with renal anemia treated in our hospital from December 2019 to December 2020 were selected and divided into experimental group (n=63) and control group (n=62) by random number table method. The control group was treated with recombinant human erythropoietin and the experimental group was treated with roxathat. Clinical efficacy, TSAT, Cys C, NOX2, erythrocyte count(RBC), hemoglobin (Hb), hematocrit (HCT), ferritin (SF), transferrin (TRF) and ferritin (HEPC) levels and the incidence of adverse drug reactions were compared between the two groups. **Results:** After treatment, the total effective rate between the two groups was significantly different (P<0.05). Before treatment, there were no significant differences in serum TSAT, Cys C and NOX2 between the experimental group and the control group. After treatment, serum TSAT in experimental group and control group increased over time, and Cys C and Nox2 in experimental group increased and decreased over time, and the difference was significant (P<0.05). Before treatment, there were no significant differences in RBC, HB and HCT test results between the experimental group and the control group. After treatment, RBC, Hb and Hct in experimental group and control group increased with the passage of time, and the difference in experimental group was significant (P<0.05). Before treatment, there were no significant differences in SF, TRF and HEPC test results between the experimental group and the control group. After treatment, serum SF and TRF of both experimental group and control group increased with time, and the experimental group was higher than the control group, and the HEPC decreased with time, and the experimental group was lower than the control group, the difference was significant (P<0.05). The total incidence of ADR in the two groups was 4.76% and 8.06%(P>0.05), respectively. **Conclusion:** The application of roxathat in patients with renal anemia has a significant effect, which may be related to the effective improvement of serum TSAT, Cys C and NOX2 levels without increasing adverse reactions.

Key words: Rosathostat; Renal anemia; Transferrin saturation; The elf inhibition; NADPH oxidase 2

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前言

肾性贫血是慢性肾脏疾病最常见的慢性并发症，是由于肾功能受损导致肾脏产生促红细胞生成素的减少而引起的，多发生在终末期肾脏病患者，且可随着疾病的严重程度而加重[1-3]。肾性贫血的发病率较高，据调查显示，慢性肾脏病尤其终末期患者肾性贫血的发生率高达 98.2%，若得不到有效治疗则可引起记忆力减退、乏力及心功能不全等并发症，甚至可能诱发心血管疾病，加重患者病情，严重影响患者预后[4,5]。目前临床通常使用重组人促红素改善患者贫血症状，但效果不佳，可长期使用可引起患者血压升高，诱发脑血管疾病[6]。罗沙司他是第二代小分子低氧诱导因子脯氨酰羟化酶（HIF-PH）抑制剂，能促进铁的吸收，综合调控肾性贫血的多个致病因素，有效改善肾性贫血[7,8]。有研究显示，肾性贫血可导致患者血清 TSAT、Cys C 及 NOX2 表达异常，因此，TSAT、Cys C 及 NOX2 可能参与了疾病的发生与发展[9]。本研究通过探讨罗沙司他治疗肾性贫血的效果，并分析其对 TSAT、Cys C 及 NOX2 的作用。

1 资料与方法

1.1 一般资料

选择 2019 年 12 月到 2020 年 12 月在我院接受治疗的 125 例肾性贫血患者，采用随机数表法分为 2 组，试验组 63 例，年龄 25-82 岁，平均（67.35± 5.63）岁，原发病：糖尿病肾病 22 例，慢性肾小球肾炎 27 例，高血压肾病 14 例；对照组 62 例，年龄 46-82 岁，平均（65.72± 5.71）岁，原发病：糖尿病肾病 20 例，肾小球肾炎 29 例，高血压肾病 13 例。两组基线资料无显著差异（P>0.05），存在可比性。

参照《肾性贫血诊断与治疗中国专家共识》[10]：Hb60~130 g/L；转铁蛋白饱和度低于 20%。

纳入标准：① 符合上述标准；② 未接受相关治疗者；③ 慢性肾脏病未规律行血液透析者；④ 签署知情同意书。排除标准：① 先天免疫性疾病者；② 神志不清者；③ 活动性溃疡者；④ 妊娠哺乳者；⑤ 心、肝功能异常者；⑥ 依从性较差者；⑦ 对本次药物过敏者；⑧ 凝血功能障碍及血液系统病变者。

1.2 方法

对照组在给予重组人促红素（规格：3000 IU/2 mL，生产厂家：上海凯茂生物医药有限公司，国药准字 S19991024）100~150 U/kg。每周 3 次注射。试验组给予罗沙司他（规格：50 mg，生产厂家：珐博进（中国）医药技术开发有限公司，国药准字 H20180023）100 mg 饭后口服，每周 3 次。

1.3 观察指标

采集空腹静脉血 5 mL，采用双抗体夹心酶联免疫吸附法测定 Cys C、NOX2 水平，采用血细胞分析仪对 RBC、Hb、Hct 进行测定，采用全自动生化分析仪测定 TSAT、SF、TRF 及 Hepc；记录不良反应发生情况。

疗效评定标准：显效：血红蛋白较治疗前上升＞30 g/L；好转：血红蛋白较治疗前上升＞15 g/L；无效：临床症状无改善。

1.4 统计学分析

以 SPSS18.0 软件包处理，符合正态分布计量资料用均数± 标准差（$\bar{x}\pm s$）表示，组间比较使用独立样本 t 检验，计数资料以率表示，x^2 检验，P＜0.05 表示差异具有统计学意义。

2 结果

2.1 不同治疗方式临床治疗效果比较

治疗后，两组总有效率比较差异显著（P<0.05）见表 1。

表 1 不同治疗方式临床治疗效果比较[n(%)]

Table 1 Comparison of clinical effects of different treatment methods[n(%)]

Groups	n	Excellent	Valid	Invalid	Total effective rate
Experimental group	63	35(55.56)	24(38.10)	4(6.35)	59(93.65)
Control group	62	28(45.16)	22(35.48)	12(19.35)	50(80.65)
x^2 value					4.735
P value					0.029

2.2 不同治疗方式 TSAT、Cys C 及 NOX2 检查结果比较

治疗前，试验组和对照组血清 TSAT、Cys C 及 NOX2 比较无显著差异；治疗后，试验组和对照组血清 TSAT 随着时间的推移而升高，且试验组高于对照组，Cys C 及 NOX2 随着时间的推移而升减降低，且试验组低于对照组，差异显著（P<0.05），见表 2。

表 2 不同治疗方式 TSAT、Cys C 及 NOX2 检查结果比较（$\bar{x}\pm s$）

Table 2 Comparison of TSAT, CYS C and NOX2 results of different treatment methods（$\bar{x}\pm s$）

Groups	n	TSAT(%)		Cys C(mg/L)		NOX2(U/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	63	18.71± 3.21	34.73± 3.45	1.84± 0.62	0.97± 0.16	53.62± 5.67	25.53± 3.91
Control group	62	18.69± 3.18	26.17± 3.29	1.86± 0.58	1.32± 0.25	54.01± 5.71	45.17± 5.89
t value		0.035	14.192	0.186	9.338	0.383	21.997
P value		0.972	0.000	0.853	0.000	0.702	0.000

2.3 不同治疗方式贫血指标检查结果对比

治疗前，试验组和对照组 RBC、Hb、Hct 检验结果比较无显著差异；治疗后，试验组和对照组 RBC、Hb、Hct 均随着时间的推移而升高，且试验组高于对照组，差异显著（P<0.05），见表 3。

表 3 不同治疗方式贫血指标检查结果对比（$\bar{x}\pm s$）

Table 3 Comparison of examination results of anemia indicators of different drug use methods（$\bar{x}\pm s$）

Groups	n	RBC（× 10^{12}/L）		Hb（g/L）		Hct（%）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	63	1.91± 0.82	3.62± 0.60	71.35± 8.37	105.05± 10.38	21.11± 2.32	36.81± 3.82
Control group	62	2.02± 0.81	2.79± 0.58	71.21± 8.29	88.62± 9.19	20.99± 2.37	29.78± 3.37
t value		0.754	7.862	0.094	9.364	0.286	10.904
P value		0.452	0.000	0.925	0.000	0.775	0.000

2.4 不同治疗方式铁代谢指标检查结果对比

治疗前，试验组和对照组 SF、TRF 及 Hepc 检验结果比较无显著差异；治疗后，试验组和对照组血清 SF、TRF 均随着时间的推移而升高，且试验组高于对照组，Hepc 随着时间的推移而下降，且试验组低于对照组，差异显著（P<0.05），见表 4。

表 4 不同治疗方式铁代谢指标检查结果对比（$\bar{x}\pm s$）

Table 4 Comparison of iron metabolism indexes in different drug use methods（$\bar{x}\pm s$）

Groups	n	SF（μg/L）		TRF（g/L）		Hepc（ng/mL）	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Experimental group	63	121.71± 20.31	289.69± 40.52	1.68± 0.41	2.81± 0.68	135.69± 53.42	95.82± 40.18
Control group	62	121.68± 20.45	217.17± 31.36	1.65± 0.39	2.18± 0.38	132.79± 50.38	121.15± 48.42
t value		0.008	11.178	0.419	6.379	0.312	3.185
P value		0.993	0.000	0.676	0.000	0.755	0.002

2.5 不同治疗方式不良反应发生情况对比

两组不良反应总发生率分别为 4.76%、8.06%（P>0.05）见表 5。

表 5 不同治疗方式不良反应发生情况对比[n（%）]

Table 5 Comparison of adverse reactions in different drug use methods[n（%）]

Groups	n	Diarrhea	Headache	Thrombosis	The total incidence of
Experimental group	63	1	1	1	3（4.76）
Control group	62	1	3	1	5（8.06）
x^2 value					0.569
P value					0.451

3 讨论

据调查报告，我国慢性肾脏病患者近 1.2 亿，患病率高达 10.8%，而肾性贫血是慢性肾脏疾病最常见的慢性并发症，是造成机体缺氧、免疫功能低下最直接因素[11,12]。长期肾性贫血患者多表现为畏寒、疲惫、肌无力、休息或活动时气促、心悸等症状，若得不到及时治疗则会导致患者发生病理变化，增加心血管疾病与死亡风险，严重威胁患者生命[13,14]。其发病机制较为复杂，现代医学认为，导致肾性贫血发生的原因有[15-17]：① 肾脏产生的促红细胞生成素生成减少；② 铁、叶酸缺乏；③ 毒素影响骨髓微环境；④ 红细胞生成抑制因子降低患者对促红细胞生成素的反应性。近年来随着医疗技术的进步，慢性肾脏疾病患者的生存期明显延长，但肾性贫血仍是影响患者健康的并发症之一[18]。

目前临床通常使用重组人促红素和铁剂治疗肾性贫血，但据相关文献显示，重组人促红素可导致患者血压异常升高及血栓的形成；而铁剂可增多机体内氧自由基释放量，减弱机体自身对铁的吸收能力，导致治疗效果不佳[19-21]。有研究显示，给予重组人促红素治疗后约 10%~20%患者血红蛋白难以达到目标[22]。缺氧诱导因子(HIF)可促进内源性促红细胞生成素分泌，刺激骨髓新红细胞的生成，罗沙司他是首个口服小分子 HIF-PHI 药物，能促进生理浓度范围内内源性重组人促红素生成，改善铁吸收，调控红细胞的生成[23-25]。有研究显示，在慢性肾病但未血液透析患者中，罗沙司他同样有较好的疗效[26]。本研究结果显示，给予罗沙司他治疗的患者有效率明显高于使用重组人促红素的患者，且两组患者不良反应发生率无明显差异，BHMSA[27]等研究中也显示，口服罗沙司他在肾性贫血的治疗

中安全性较高,无明显副作用,与本研究结果相似。肾性贫血常由于营养不良,导致铁代谢紊乱,临床通常使用 SF、TRF、Hepc 作为评价铁代谢的指标[28]。SF 是反映缺铁性红细胞生成的指标;Hepc 由肝脏分泌的,参与免疫反应,机体内的铁水平会对其产生影响[29]。本研究显示,治疗后患者 RBC、Hb、Hct、SF、TRF 明显升高,Hepc 明显降低,但给予罗沙司他治疗的患者 RBC、Hb、Hct、SF、TRF 高于对照组,Hepc 低于对照组,提示,罗沙司他治疗肾性贫血效果显著,可改善患者贫血症状及铁代谢指标。Mizuno K[30]等研究显示,罗沙司他可改善铁的吸收利用,降低铁调素水平,抑制红细胞生成,改善患者铁代谢,对改善患者贫血具有重要意义。分析其原因可能是因为罗沙司他作为 HIF-PHI 药物,能抑制 HIF 降解,降低 Hepc 水平,增强肠道对铁的吸收,提高 TRF 受体活性,而重组人促红素则仅能增加患者体内重组人促红素水平。

有研究显示,多种血清在肾性贫血中表达异常,参与了疾病的发展[31]。TSAT 代表可供给骨髓利用铁的数量,是铁生物利用的临床指标,合理高水平有助于减少透析患者血红蛋白波动[32]。贫血可加重肾功能损伤,影响红细胞正常代谢,加重贫血程度,因此改善贫血患者肾功能具有重要意义[33]。Cys C 是评估肾功能较为敏感的指标,由有核细胞以恒速产生,从肾小球滤过的同时能被肾小管上皮细胞完全重吸收[34]。氧化应激参与了多种肾脏疾病的发展,氧化应激水平是由细胞抗氧化系统与活性氧间的平衡决定的,肾脏缺血产生的活性氧是促进肾小管损伤的主要因素,NOX 是活性氧生成的主要酶体,NOX2 主要存在于吞噬细胞中,在缺血状态下低氧刺激可诱导产生 ROS,在肾功能损伤时其水平异常升高[35]。本研究将 TSAT、Cys C 及 NOX2 作为参与肾性贫血的重要指标,观察在治疗期间水平变化,结果显示,治疗后患者血清 TSAT 明显升高,Cys C 及 NOX2,且给予罗沙司他治疗的患者 TSAT 高于对照组,Cys C 及 NOX2 低于对照组,进一步说明了罗沙司他可改善肾性贫血患者 TSAT、Cys C 及 NOX2 水平。分析其原因可能是因为罗沙司他可促进红细胞生成,降低血清铁蛋白,通过改善患者铁含量,间接改善 TSAT 水平。但本研究纳入样本量较小,可导致研究结果出现误差,对疗效具有一定的局限性,今后应进一步深入探究罗沙司他治疗肾性贫血患者 TSAT、Cys C 及 NOX2 的影响,为远期疗效的研究工作打好基础。

综上所述,在肾性贫血患者中应用罗沙司他效果显著,可能与其可有效改善血清 TSAT、Cys C 及 NOX2 水平有关,且不增加不良反应。

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（上接第 4675 页）

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