

doi: 10.13241/j.cnki.pmb.2020.11.033

白蛋白静脉滴注联合茵栀黄颗粒治疗新生儿黄疸血清 AKP、TBA、FFA、 γ -GT、HS-CRP 的影响 *

杜喜维¹ 杨瑞霞¹ 晋亚楠¹ 孙 宝¹ 杨 越¹ 曹小雨¹ 赵 宏^{2Δ}

(1 西安医学院第二附属医院药剂科 陕西 西安 710038; 2 西电集团医院新生儿科 陕西 西安 710077)

摘要 目的: 研究白蛋白静脉滴注联合茵栀黄颗粒对新生儿黄疸血清碱性磷酸酶 (alkaline phosphatase, AKP)、总胆汁酸 (total bile acids, TBA)、游离脂肪酸 (free fatty acid, FFA)、 γ -谷氨酰基转移酶 (γ -glutamyltransferase, γ -GT)、超敏 C-反应蛋白 (hypersensitive C-reactive protein, HS-CRP) 的影响。**方法:** 选择 2016 年 1 月~2019 年 1 月我院收治的 95 例新生儿病理性黄疸患儿, 随机分为两组。对照组服用茵栀黄颗粒治疗, 观察组在服用茵栀黄的基础上静脉滴注白蛋白治疗。检测两组的血清间接胆红素 (indirect reacting bilirubin, IBIL)、总胆红素 (total bilirubin, TBIL) 和 AKP、TBA、FFA、 γ -GT、HS-CRP 水平。**结果:** 观察组的有效率明显高于对照组 ($P<0.05$); 两组治疗后的血清 IBIL、TBIL 水平明显降低 ($P<0.05$), 观察组的 IBIL、TBIL 水平明显低于对照组 ($P<0.05$); 两组治疗后的血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平明显降低 ($P<0.05$), 观察组的血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平明显低于对照组 ($P<0.05$)。**结论:** 白蛋白静脉滴注联合茵栀黄颗粒对新生儿黄疸的治疗效果良好, 有助于促进血清胆红素和其他血清学相关指标恢复正常, 且安全性好。

关键词: 新生儿黄疸; 白蛋白; 茵栀黄颗粒; 血清学指标

中图分类号: R722.1 文献标识码: A 文章编号: 1673-6273(2020)11-2152-04

Effect of Albumin Intravenous Drip Combined with Yinzhihuang Granule on Serum AKP, TBA, FFA, Gamma-GT and HS-CRP in Neonates with Jaundice*

DU Xi-wei¹, YANG Rui-xia¹, JIN Ya-nan¹, SUN Bao¹, YANG Yue¹, CAO Xiao-yu¹, ZHAO Hong^{2Δ}

(1 Department of Pharmacy, The Second Affiliated Hospital of Xi'an Medical College, Xi'an, Shaanxi, 710038, China;

2 Department of Neonatology, Xi'an XD Group Hospital, Xi'an, Shaanxi, 710077, China)

ABSTRACT Objective: To study the effects of intravenous albumin infusion combined with Yinzhihuang Granule on serum alkaline phosphatase (AKP), total bile acids (TBA), free fatty acid (FFA), γ -glutamyltransferase (γ -GT) and hypersensitive C-reactive protein (HS-CRP) in neonates with jaundice. **Methods:** 95 children with neonatal jaundice to our hospital from January 2016 to January 2019, divided into two groups randomly. The control group was treated with Yinzhihuang Granule, and the observation group was treated with intravenous drip of albumin on the basis of Yinzhihuang. Indirect reactive bilirubin (IBIL), total bilirubin (TBIL), and AKP, TBA, FFA, γ -GT, and HS-CRP levels were measured in two groups. **Results:** The effective rate of the observation group was significantly higher than control group ($P<0.05$). After treatment, the levels of IBIL and TBIL in the two groups decreased significantly ($P<0.05$), and the observation group were significantly lower than those in the control group ($P<0.05$). The serum AKP, TBA, FFA, gamma-GT and HS-CRP levels in the two groups were significantly decreased after treatment ($P<0.05$), and the serum AKP, TBA, FFA, gamma-GT and HS-CRP levels in the observation group were significantly lower than those in the control group ($P<0.05$). **Conclusion:** Albumin combined with Yinzhihuang Granule has a good therapeutic effect on neonatal jaundice, which is helpful to promote the recovery of serum bilirubin and other serological related indicators, and has good safety.

Key words: Neonatal jaundice; Albumin; Yinzhihuang granules; Serological indicators

Chinese Library Classification(CLC): R722.1 **Document code:** A

Article ID: 1673-6273(2020)11-2152-04

前言

黄疸是新生儿期极为常见的一种症状, 主要是由于胆红素

代谢出现异常, 造成胆红素大量聚集于黏膜、皮肤等部位而出现黄疸的临床病症^[1,2]。大多数的早产儿或者健康足月儿在出生后均有可能出现新生儿黄疸。如果黄疸症状反复出现或者持续

* 基金项目: 陕西省科技厅基金项目 (2017SF-093)

作者简介: 杜喜维 (1984-), 女, 硕士研究生, 主管药师, 研究方向: 临床药学, 电话: 15109288993, E-mail: duxiwei1234@163.com

Δ 通讯作者: 赵宏 (1974-), 女, 本科, 副主任医师, 研究方向: 新生儿, 电话: 13700232931, E-mail: 1012064567@qq.com

(收稿日期: 2019-10-27 接受日期: 2019-11-23)

不退,均为病理性黄疸。一旦新生儿发生病理性黄疸,需要给予积极的治疗方法,否则容易引起胆红素脑病,导致患儿的神经系统功能的严重受损,甚至引发死亡^[3-5]。新生儿黄疸患儿体内不仅血清胆红素增高,还会出现 AKP、TBA、FFA、 γ -GT、HS-CRP 水平升高,这些指标在该病的病情发展中有一定的指示作用^[6]。儿科医师需高度重视新生儿黄疸。目前认为通过采取科学合理的干预可以使新生儿未结合的胆红素水平明显降低,有效预防胆红素脑病,而对于方法的探索及选择是临床研究的焦点问题^[7]。白蛋白作为胆红素载体中的一种,可与 E 型胆红素稳定地进行结合,形成具有较高亲水性的结合胆红素,经过胆汁尿液排出机体外^[8,9];而且,有学者认为其在黄疸的预防中具有较好的作用^[10]。近年来,随着中西医结合治疗的发展,取得了较好的疗效,茵栀黄颗粒具有清热、解毒、利湿、退黄的作用,用于治疗新生儿黄疸,患儿易接受。本研究创新性地将白蛋白与茵栀黄颗粒联用,分析其对新生儿黄疸的疗效。

1 资料与方法

1.1 研究对象

选择 2016 年 1 月~2019 年 1 月我院的 95 例新生儿病理性黄疸患儿,纳入标准:均符合《实用新生儿学》的标准;对白蛋白和茵栀黄颗粒不过敏;为足月正常的新生儿,而且出生后仅采取母乳喂养。排除标准:出现过缺血性脑病或者宫内缺氧的患儿;患有先天畸形、先天性心脏病、先天性白内障等先天性疾病的患儿;患有重度窒息、呼吸窘迫综合征、头颅血肿等的患儿。用抽签法随机分为两组。观察组 47 例,男 25 例,女 22 例;年龄 4~38 d,平均 (17.42 ± 5.29) d;出生体质量 2.34~4.59 kg,

平均 (3.29 ± 0.45) kg。对照组 48 例,男 27 例,女 21 例;年龄 4~38 d,平均 (17.65 ± 4.23) d;出生体质量 2.29~4.67 kg,平均 (3.31 ± 0.38) kg。两组的基线资料具有可比性。

1.2 治疗方法

患儿入院后均给予抗感染、维持水电解质及酸碱平衡、营养支持、吸氧和保暖、蓝光照射、保肝等常规疗法。对照组服用茵栀黄颗粒,每次 1/4 袋,每天 3 次;观察组在服用茵栀黄的基础上,将 1.0 g/kg 白蛋白用 15 mL 10% 的葡萄糖溶液进行稀释,每天静脉滴注 1 次。两组均治疗 3 d。

1.3 观察指标

疗效标准:① 治愈:患儿的巩膜及黏膜、皮肤黄染消失,胆红素水平基本恢复正常,随访 6 个月未出现复发;② 有效:患儿的巩膜及黏膜、皮肤黄染明显减轻,胆红素水平明显降低,但是仍然高于正常水平,需要进行继续治疗;③ 无效:患儿的巩膜及黏膜、皮肤黄染未减轻,胆红素水平为降低。

检测两组治疗前后的血清间接胆红素 (IBIL)、总胆红素 (TBIL) 水平,及其他相关的血清指标:AKP、TBA、FFA、 γ -GT、HS-CRP。

对比两组治疗期间不良反应发生情况。

1.4 统计方法

采用 SPSS19.00,计量数据以 $(\bar{x} \pm s)$,计数数据以 % 表示,对比采用 t 检验与卡方分析,检验水准为 $\alpha=0.05$ 。

2 结果

2.1 疗效比较

观察组的治疗总有效率高于对照组 ($P<0.05$),见表 1。

表 1 疗效比较[例(%)]

Table 1 Comparison of the clinical effect[n(%)]

Groups	n	Cure	Valid	Invalid	The total effect rate
Control group	48	24(50.00)	11(22.92)	13(27.08)	72.92
Observation group	47	31(65.96)	14(29.79)	2(4.25)	95.74*

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

2.2 血清 IBIL、TBIL 水平比较

两组治疗后的 IBIL、TBIL 水平明显降低 ($P<0.05$),观察组

的 IBIL、TBIL 水平明显低于对照组 ($P<0.05$),见表 2。

表 2 血清 IBIL、TBIL 水平比较($\bar{x} \pm s, \mu\text{mol/L}$)

Table 2 Comparison of serum IBIL and TBIL levels($\bar{x} \pm s, \mu\text{mol/L}$)

Groups	n	TBIL		IBIL	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	48	204.39 $\pm$ 11.72	149.36 $\pm$ 9.48 [#]	178.24 $\pm$ 8.36	154.32 $\pm$ 7.31 [#]
Observation group	47	205.83 $\pm$ 10.14	115.26 $\pm$ 7.34* [#]	177.32 $\pm$ 8.45	114.38 $\pm$ 6.21* [#]

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

2.3 血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平比较

两组治疗后的血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平明显降低 ($P<0.05$),且观察组低于对照组 ($P<0.05$),见表 3。

2.4 不良反应

对照组发生 2 例发热、1 例皮疹及 2 例腹泻;观察组发生 2

例腹泻及 2 例发热;两组无明显差异 ($P>0.05$)。两组在治疗期间均未停止用药治疗,停药后不良反应基本消失。

3 讨论

血液中的胆红素主要来源于肠肝循环以及血红蛋白,因为

新生儿机体内红细胞的寿命比较短,使其来源于血红蛋白的量明显减少,进而促进胆红素的肠肝循环量大大增加,造成大量的胆红素积聚在机体内^[11-13]。加上新生儿的排泄能力比较差,相关的代谢酶菌尚未成熟,胆红素的排出速度比较慢,从而造成新生儿出生后极容易出现胆红素水平升高,最新导致黄疸^[14-16]。生理性黄疸无需治疗,会在出生后大约 2 周时间自行消退。但是有部分的新生儿尤其是早产儿因为自身的消化功能以

及免疫功能较低,造成胆红素在血清中引发不良反应,此类黄疸称为病理性黄疸^[17,18]。新生儿败血症、细菌感染、病毒感染(乙型肝炎病毒和甲型肝炎病毒等)都能导致新生儿病理性黄疸。若未及时治疗病理性黄疸,则容易引起寒战、发热、恶心呕吐、血红蛋白尿、贫血,甚至导致永久性脑损伤以及急性肾衰竭等,对患儿的神经系统造成损伤,对生长发育造成不利影响^[19-21]。

表 3 血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平比较($\bar{x} \pm s$)
Table 3 Comparison of serum AKP, TBA, FFA, gamma-GT and HS-CRP levels($\bar{x} \pm s$)

Groups	n	AKP(U/L)		TBA(μ mol/L)		FFA(μ mol/L)		γ -GT(U/L)		HS-CRP(mg/L)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	48	245.31 $\pm$ 27.86	153.72 $\pm$ 14.63 [#]	33.27 $\pm$ 6.45	16.39 $\pm$ 4.21 [#]	4207.36 $\pm$ 257.36	2005.79 $\pm$ 143.26 [#]	143.25 $\pm$ 13.78	87.42 $\pm$ 9.34 [#]	3.34 $\pm$ 0.42	1.23 $\pm$ 0.27 [#]
Observation group	47	244.57 $\pm$ 26.93	103.24 $\pm$ 11.35 ^{*#}	32.84 $\pm$ 5.92	9.34 $\pm$ 3.25 ^{*#}	4206.54 $\pm$ 263.48	1849.26 $\pm$ 107.23 ^{*#}	144.25 $\pm$ 12.73	48.36 $\pm$ 7.21 ^{*#}	3.35 $\pm$ 0.39	0.57 $\pm$ 0.14 ^{*#}

茵栀黄颗粒的成分包括栀子、茵陈、金银花和黄芩等,方中栀子具有泻火除烦和清热利湿的效果^[22]。茵陈具有退黄疸和清热利湿的效果,药理学研究表明,茵陈能保护机体的肝脏,具有抗炎症反应及解热的效果,能加速黄疸患儿胆汁的分泌,增加胆汁中固体的排出量,扩张胆管,促进胆汁的分泌^[23,24]。黄芩具有泻火解毒、清热燥湿、利尿和止血的效果。该药物用于成人,则主要用在肝胆湿热所致的黄疸,症见胸胁胀痛,面目悉黄,小便黄赤,恶心呕吐,而对新生儿黄疸也能取得较佳的疗效。但单独使用的效果并不佳。白蛋白能与 E 型胆红素发生结合,进而有效稳定 E 型胆红素,防止其反转录成 Z 型胆红素^[25-27]。静脉滴注白蛋白能使 E 型胆红素与白蛋白结合的机会大大增加,防止由于 E 型胆红素不稳定而重新逆转为 Z 型胆红素,进而达到稳定以及加强治疗效果的目的^[28-32]。观察组的有效率明显高于对照组;表明白蛋白静脉滴注在协同茵栀黄颗粒治疗新生儿黄疸方面的临床效果比较显著。

AKP 主要在成骨过程中水解焦磷酸盐和磷酸酯,消除焦磷酸盐抑制骨盐形成的效果。 γ -GT 主要用于评估肝胆疾病,是肝炎活动即胆道梗阻的指标,轻度和中度 γ -GT 升高者主要见于肝硬化、病毒性肝炎和胰腺炎等。HS-CRP 是患者受到炎症性的刺激时,机体的肝细胞合成的一种急性相蛋白,在出现炎症的数小时,HS-CRP 就会明显升高,48 小时就能达到峰值,随着病变的消退、组织的功能及结构的恢复而降低为正常的水平。新生儿黄疸时,除了会引起总胆红素升高之外,血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平变化^[6]。当黄疸加重时,血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平也上升。因而,上述的血清学指标与其严重程度有关。新生儿的免疫力低下、消化功能低下以及肠道内细菌少等,使未结合的胆红素重新被机体吸收,造成血清 HS-CRP、胆红素水平升高。两组治疗后的血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平明显降低,观察组明显更低。表明在服用茵栀黄颗粒的基础上联用白蛋白更有助于促进患儿康复,其机制可能与降低血清 AKP、TBA、FFA、 γ -GT、HS-CRP 水平有关。

综上所述,白蛋白静脉滴注联合茵栀黄颗粒对新生儿黄疸的治疗效果良好,有助于促进血清胆红素和其他血清学相关指标恢复正常,且安全性好。

参考文献(References)

- [1] Olusanya BO, Teeple S, Kassebaum NJ. The Contribution of Neonatal Jaundice to Global Child Mortality: Findings From the GBD 2016 Study[J]. Pediatrics, 2018, 141(2): e20171471
- [2] Wu RH, Feng S, Mei H, et al. Yinzhihuang oral liquid combined with phototherapy for neonatal jaundice: a systematic review and meta-analysis of randomized clinical trials[J]. BMC Complement Altern Med, 2018, 18(1): 228-249
- [3] Prins TJ, Triphoving M, Paw MK, et al. A Survey of Practice and Knowledge of Refugee and Migrant Pregnant Mothers Surrounding Neonatal Jaundice on the Thailand-Myanmar Border [J]. J Trop Pediatr, 2017, 63(1): 50-56
- [4] Hodgson JM, Someren V HV, Smith C, et al. Direct bilirubin levels observed in prolonged neonatal jaundice: a retrospective cohort study [J]. BMJ Paediatr Open, 2018, 2(1): e000202
- [5] Santos SE, Moreira SH, Azevedo LL, et al. Clinical practices among healthcare professionals concerning neonatal jaundice and pale stools [J]. Eur J Pediatr, 2017, 176(3): 361-369
- [6] 尹欢,程红斌. 白蛋白静脉滴注复合蓝光照治疗新生儿黄疸的疗效观察[J]. 中国妇幼保健, 2017, 32(22): 258-260
- [7] Orimadegun AE, Ojebiyi AO. Primary health workers' knowledge and practices relating to neonatal jaundice in Ibadan, Nigeria [J]. Afr J Prim Health Care Fam Med, 2017, 9(1): e1
- [8] Geng T, Zhao X, Ma M, et al. Resveratrol-Loaded Albumin Nanoparticles with Prolonged Blood Circulation and Improved Biocompatibility for Highly Effective Targeted Pancreatic Tumor Therapy [J]. Nanoscale Res Lett, 2017, 12(1): 437-454
- [9] Sun P, Chen C, Xia Y, et al. The Ratio of C-Reactive Protein/Albumin is a Novel Inflammatory Predictor of Overall Survival in Cisplatin-Based Treated Patients with Metastatic Nasopharyngeal Carcinoma[J]. Dis Markers, 2017, 2017(11): e6570808

- [10] Dzi C, Zinman B, Inzucchi SE, et al. Effects of empagliflozin on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and established cardiovascular disease: an exploratory analysis from the EMPA-REG OUTCOME randomised, placebo-controlled trial[J]. *Lancet Diabetes Endocrinol*, 2017, 5(8): 610-621
- [11] Monsef A, Eghbalian F, Rahimi N. Comparison of Purgative Manna Drop and Phototherapy with Phototherapy Treatment of Neonatal Jaundice: A Randomized Double-Blind Clinical Trial[J]. *Osong Public Health Res Perspect*, 2019, 10(3): 152-157
- [12] Yang L, Wu, Wang B, et al. The influence of zinc sulfate on neonatal jaundice: a systematic review and meta-analysis [J]. *J Matern Fetal Neonatal Med*, 2017, 31(10): 1311-1317
- [13] Keahey PA, Simeral ML, Schroder KJ, et al. Point-of-care device to diagnose and monitor neonatal jaundice in low-resource settings[J]. *Proc Natl Acad Sci USA*, 2017, 114(51): E10965-E10971
- [14] Adoba P, Ephraim R KD, Kontor KA, et al. Knowledge Level and Determinants of Neonatal Jaundice: A Cross-Sectional Study in the Effutu Municipality of Ghana[J]. *Int J Pediatr*, 2018, 2018(2): 1-9
- [15] Hussain AS, Shah MH, Lakhdir M, et al. Effectiveness of transcutaneous bilirubin measurement in managing neonatal jaundice in post-natal ward of a tertiary care hospital in Pakistan [J]. *BMJ Paediatrics Open*, 2017, 1(1): e000065
- [16] Jiao Y, Jin Y, Meng H, et al. An analysis on treatment effect of blue light phototherapy combined with Bifico in treating neonatal hemolytic jaundice[J]. *Exp Ther Med*, 2018, 16(2): 1360-1364
- [17] Pasha YZ, Kacho MA, Niaki HA, et al. The Association between Prolonged Jaundice and TATA Box Dinucleotide Repeats in Gilberts Syndrome[J]. *J Clin Diag Res*, 2017, 11(9): GC05-GC07
- [18] Fawaz R, Baumann U, Ekong U, et al. Guideline for the Evaluation of Cholestatic Jaundice in Infants: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology [J]. *J Pediatr Gastroenterol Nutr*, 2017, 64(1): 154-168
- [19] Shapiro S, Le PJ, Riordan SM, et al. The Neurological Sequelae of Neonatal Hyperbilirubinemia: Definitions, Diagnosis and Treatment of the Kernicterus Spectrum Disorders (KSDs) [J]. *Curr Pediatr Rev*, 2017, 13(3): 199-209
- [20] Tola HH, Ranjbaran M, Omani-Samani R, et al. Prevalence of UTI among Iranian infants with prolonged jaundice, and its main causes: A systematic review and meta-analysis study[J]. *J Pediatr Urol*, 2018, 14(2): 108-115
- [21] Zanardo V, Luca FD, Simbi AK, et al. Umbilical cord blood acid-base analysis and the development of significant hyperbilirubinemia in near-term and term newborns: a cohort study [J]. *Ital J Pediatr*, 2017, 43(1): 67-80
- [22] Wu RH, Feng S, Mei H, et al. Yinzhihuang oral liquid combined with phototherapy for neonatal jaundice: a systematic review and meta-analysis of randomized clinical trials[J]. *BMC Complement Altern Med*, 2018, 18(1): 228-249
- [23] Liu H, Sun W, Gu LB, et al. Huaqiqi Huang Granules, reduce proteinuria by enhancing nephrin expression and regulating necrosis factor κ B signaling pathway in adriamycin-induced nephropathy[J]. *Chinese Journal of Integrative Medicine*, 2017, 23(4): 41-49
- [24] Liu H, Sun W, Gu LB, et al. Huaqiqi Huang Granules reduce proteinuria by enhancing nephrin expression and regulating necrosis factor κ B signaling pathway in adriamycin-induced nephropathy [J]. *Chinese Journal of Integrative Medicine*, 2017, 23(4): 279-287
- [25] Huang Q, Wang S, Jie Z, et al. Albumin-assisted exfoliated ultrathin rhodium disulfide nanosheets as a tumor targeting and dual-stimuli-responsive drug delivery system for a combination chemo-photothermal treatment[J]. *RSC Advances*, 2018, 8(9): 4624-4633
- [26] Chaves OA, Silva VAD, Sant'Anna CMR, et al. Binding studies of lophirone B with bovine serum albumin (BSA): Combination of spectroscopic and molecular docking techniques [J]. *Journal of Molecular Structure*, 2017, 1128(Complete): 606-611
- [27] Fung CSC, Wan EYF, Chan AKC, et al. Association of estimated glomerular filtration rate and urine albumin-to-creatinine ratio with incidence of cardiovascular diseases and mortality in chinese patients with type 2 diabetes mellitus - a population-based retrospective cohort study[J]. *Bmc Nephrology*, 2017, 18(1): 47-67
- [28] Haste P, Tann M, Persohn S, et al. Correlation of Technetium-99m Macroaggregated Albumin and Yttrium-90 Glass Microsphere Biodistribution in Hepatocellular Carcinoma: A Retrospective Review of Pretreatment Single Photon Emission CT and Posttreatment Positron Emission Tomography/CT [J]. *J Vasc Interv Radiol*, 2017, 28(5): 722-730
- [29] Yasuda Y, Hattori Y, Tohrai R, et al. The safety and efficacy of carboplatin plus nanoparticle albumin-bound paclitaxel in the treatment of non-small cell lung cancer patients with interstitial lung disease[J]. *Jpn J Clin Oncol*, 2017, 48(1): 1-5
- [30] Sanyal AJ, Boyer TD, Frederick RT, et al. Reversal of hepatorenal syndrome type 1 with terlipressin plus albumin vs. placebo plus albumin in a pooled analysis of the OT-0401 and REVERSE randomised clinical studies[J]. *Aliment Pharmacol Ther*, 2017, 45(11): 1390-1402
- [31] Lin Y, Linask KL, Mallon B, et al. Heparin Promotes Cardiac Differentiation of Human Pluripotent Stem Cells in Chemically Defined Albumin-Free Medium, Enabling Consistent Manufacture of Cardiomyocytes[J]. *Stem Cells Transl Med*, 2017, 6(2): 527-538
- [32] Yin MM, Dong P, Chen WQ, et al. Thermodynamics and Mechanisms of the Interactions between Ultrasmall Fluorescent Gold Nanoclusters and Human Serum Albumin, γ -Globulins, and Transferrin: A Spectroscopic Approach[J]. *Langmuir*, 2017, 33(21): 5108-5116