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腺苷蛋氨酸联合白蛋白治疗新生儿黄疸的临床疗效及对血清 γ -谷氨酰转移酶、胰岛素样生长因子水平的影响*

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摘要 目的:探讨腺苷蛋氨酸联合白蛋白治疗新生儿黄疸的临床疗效及对患儿血清 γ -谷氨酰转移酶、胰岛素样生长因子水平的影响。方法:选取2017年3月至2019年3月我院收治的203例新生儿黄疸患儿,按照随机数表法分为观察组(n=105)和对照组(n=98)。对照组采用白蛋白治疗,观察组采用腺苷蛋氨酸联合白蛋白治疗。观察及对比两组治疗疗效,黄疸消退时间及黄疸指数水平,治疗前后胆红素各项指标、 γ -谷氨酰转移酶、胰岛素样生长因子、转铁蛋白水平的变化。结果:治疗后,观察组总有效率显著高于对照组 [92.38%(97/105) vs. 80.61%(79/98)] ($P<0.05$); 黄疸消退时间及黄疸指数水平均显著低于对照组 [(4.15 $\pm$ 0.82) d vs. (5.31 $\pm$ 0.92) d, (56.02 $\pm$ 7.36) μ mol/L vs. (82.86 $\pm$ 9.32) μ mol/L] ($P<0.05$); 间接胆红素、结合胆红素、总胆红素水平均显著低于对照组 [(108.75 $\pm$ 6.21) d vs. (146.03 $\pm$ 7.32) d, (7.49 $\pm$ 0.85) μ mol/L vs. (9.57 $\pm$ 1.02) μ mol/L, (117.80 $\pm$ 6.52) μ mol/L vs. (151.09 $\pm$ 8.34) μ mol/L] ($P<0.05$); γ -谷氨酰转移酶、胰岛素样生长因子均显著低于对照组 [(56.01 $\pm$ 6.45) U/L vs. (89.56 $\pm$ 10.73) U/L, (19.30 $\pm$ 2.17) ng/L vs. 26.78 $\pm$ 3.67 ng/L] ($P<0.05$); 而转铁蛋白水平均显著高于对照组 [(1.96 $\pm$ 0.27) g/L vs. (1.60 $\pm$ 0.24) g/L] ($P<0.05$)。结论:腺苷蛋氨酸联合白蛋白治疗新生儿黄疸的临床疗效显著优于单用白蛋白治疗,其可有效改善患儿的黄疸临床症状,降低血清胆红素、 γ -谷氨酰转移酶、胰岛素样生长因子水平。

关键词: 腺苷蛋氨酸; 白蛋白; 新生儿黄疸; γ -谷氨酰转移酶; 胰岛素样生长因子

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Clinical Efficacy of Adenosylmethionine Combined with Albumin in the Treatment of Neonatal Jaundice and Its Effect on the Serum γ -glutamyltransferase and Insulin-like Growth Factor Levels*

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ABSTRACT Objective: To explore the clinical efficacy of adenosylmethionine combined with albumin in the treatment of neonatal jaundice and its effect on the levels of serum γ -glutamyltransferase and insulin-like growth factor in children. **Methods:** 203 cases of newborns with neonatal jaundice admitted to our hospital from March 2017 to March 2019 were selected, According to the method of random number table, they were divided into the observation group (n=105) and the control group (n=98). The control group was treated with albumin, while the observation group treated with adenosylmethionine combined with albumin. The therapeutic effect, jaundice regression time and jaundice index, changes of bilirubin indexes, γ -glutamyltransferase, insulin-like growth factor and transferrin level before and after treatment were observed and compared between two groups. **Results:** After treatment, the total effective rate of observation group was significantly higher than that of the control group [92.38%(97/105) vs. 80.61%(79/98)] ($P<0.05$). Jaundice regression time and jaundice index were significantly lower than the control group [(4.15 $\pm$ 0.82) d vs. (5.31 $\pm$ 0.92) d, (56.02 $\pm$ 7.36) μ mol/L vs. (82.86 $\pm$ 9.32) μ mol/L] ($P<0.05$). The levels of indirect bilirubin, conjugated bilirubin and total bilirubin were significantly lower than those of the control group [(108.75 $\pm$ 6.21) d vs. (146.03 $\pm$ 7.32) d, (7.49 $\pm$ 0.85) μ mol/L vs. (9.57 $\pm$ 1.02) μ mol/L, (117.80 $\pm$ 6.52) μ mol/L vs. (151.09 $\pm$ 8.34) μ mol/L] ($P<0.05$). γ -glutamyltransferase and insulin-like growth factor were significantly lower than those in the control group [(56.01 $\pm$ 6.45) U/L vs. (89.56 $\pm$ 10.73) U/L, (19.30 $\pm$ 2.17) ng/L vs. 26.78 $\pm$ 3.67 ng/L] ($P<0.05$). The level of transferrin was significantly higher than that of the control group [(1.96 $\pm$ 0.27) g/L vs. (1.60 $\pm$ 0.24) g/L] ($P<0.05$). **Conclusion:** The clinical effect of adenosylmethionine combined with albumin in the treatment of neonatal jaundice is significantly better than that of albumin alone. It can effectively improve the clinical symptoms of jaundice in children, and reduce the levels of serum bilirubin, γ -glutamyltransferase

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and insulin-like growth factor.

Key words: Adenosylmethionine; Albumin; Jaundice of the newborn; Gamma glutamyltransferase; Insulin like growth factor

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前言

黄疸是新生儿常见疾病,是新生儿时期出现的胆红素代谢异常,血中胆红素水平升高使新生儿的皮肤、黏膜及巩膜黄染为特征^[1]。胆红素具有一定的毒性,当患儿长期处于高胆红素状态时,或较多的胆红素进入细胞影响正常细胞的代谢,胆红素血症会引发胆红素脑病,对神经系统造成的毒性,影响新生儿的基底神经节、耳蜗核及动眼神经核团,不利于新生儿的健康成长^[2]。研究显示新生儿在出生后1周内的黄疸发生率高达80%及以上^[3]。因此,降低新生儿黄疸的发生率是目前医学界的一大努力方向。

蓝光照射是临床上治疗新生儿黄疸的常用方法,虽可改善新生儿的黄疸症状,但未达到满意的疗效^[4]。白蛋白是人体内一种重要的营养物质,可保证细胞内液、细胞外液及组织液间交流,可稳定蛋白球。腺苷蛋氨酸能够治疗肝内胆汁淤积,具有保护肝脏,促进黄疸消退的作用^[5]。本研究旨在探讨腺苷蛋氨酸联合白蛋白治疗新生儿黄疸的临床疗效及其可能机制,现报道如下。

1 资料与方法

1.1 一般资料

收集203例新生儿黄疸患儿,均符合《褚福棠实用儿科学》中新生儿病理性黄疸的诊断标准。纳入标准^[6]:出生后24 h内出现黄疸;黄疸呈进行性加重;黄疸持续时间超过2周;患儿家属同意本研究并签署知情同意书;排除标准:伴有先天性严重疾病;伴有胆道疾病;对本次治疗药物过敏者;患有严重肺炎。按照随机数表法将所有患者分为观察组(n=105)和对照组(n=98)。观察组中,男63例,女42例,胎龄36~41周,平均(39.56±0.72)岁,日龄2~21 d,平均日龄(13.56±2.61)d,出生体质量2.6~4.1 kg,平均体质量(3.21±0.35)kg,黄疸发生时间3~20 d,平均时间(11.09±2.78);对照组中,男57例,女41例,胎龄37~41周,平均(40.02±0.75)岁,日龄3~20 d,平均日龄(12.97±2.58)d,出生体质量2.7~4.2 kg,平均体质量(3.22±0.34)kg,黄疸发生时间3~21 d,平均时间(12.03±2.85)。两组患儿一般资料比较均无明显差异($P>0.05$),具有可比性。

1.2 治疗方法

两组患者均放置于蓝光治疗箱内,采用黑布遮盖双眼、会阴及肛门等部位,其他部位进行裸露照射,每次照射时间为12 h,每天1次,治疗疗程为7 d。对照组在此基础上采用白蛋白(生产厂家:珠海海吉尔生物制品有限公司)静脉滴注治疗,将1 g/kg白蛋白与10%葡萄糖溶液15~20 mL溶合,合理调节输液泵滴速,以先慢渐缓的方式静脉滴注。观察组在对照组的基础上采用丁二磺酸腺苷蛋氨酸肠溶(生产厂家:浙江海正药业股份有限公司)治疗,每天80 kg,7 d为一个治疗疗程。若患儿血清游离胆红素浓度 $>320 \mu\text{mol/L}$,采用静脉滴注清蛋白或血浆用以支持,若患儿出现溶血,采用部分换血治疗。

1.3 观察指标

观察两组治疗疗效,黄疸消退时间及黄疸指数水平,胆红素各项指标水平, γ -谷氨酰转移酶、胰岛素样生长因子、转铁蛋白水平变化。

1.3.1 指标检测 分别于治疗前后采集5 mL静脉血,离心分离血清,采用钼酸盐氧化法检测间接胆红素、结合胆红素、总胆红素水平,采用全自动生化分析仪检测;采用酶联免疫吸附法检测 γ -谷氨酰转移酶、胰岛素样生长因子、转铁蛋白水平, γ -谷氨酰转移酶试剂盒购于上海拜力生物科技有限公司,胰岛素样生长因子试剂盒购于上海丰寿生物科技有限公司,试剂盒购自北京普赞生物技术有限公司。

1.3.2 疗效评定标准 血清胆红素水平恢复正常,黄疸症状完全消失且未复发为治愈^[7]。血清胆红素水平明显下降,黄疸症状有所缓解为有效;血清胆红素水平无明显变化,黄疸症状仍明显为无效。

1.4 统计学分析

使用SPSS18.0统计软件进行统计,数据均符合正态分布,计数资料以[(例)%]表示,组间比较采用 χ^2 检验,计量资料以($\bar{x} \pm s$)表示,组间比较采用成组t检验,组内比较使用配对样本t检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组治疗疗效的比较

治疗后,观察组总有效率为92.38%,显著高于对照组($P<0.05$),见表1。

表1 两组治疗疗效的比较[例(%)]

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

Groups	Recovery	Improve	Invalid	Total effective rate
Observation group(n=105)	66(62.85)	31(29.52)	8(7.61)	97(92.38)
Control group(n=98)	52(53.06)	27(27.55)	19(19.38)	79(80.61)

2.2 两组黄疸消退时间及黄疸指数水平的比较

两组治疗前黄疸指数水平比较差异无统计学意义($P>0.05$),两组治疗后黄疸指数均较治疗前显著降低,且观察组显著

低于对照组($P<0.05$),且观察组黄疸消退时间显著短于对照组($P<0.05$),见表2。

表 2 两组黄疸消退时间及黄疸指数水平变化情况的比较($\bar{x} \pm s$)

Table 2 Comparison of the jaundice regression time and changes of jaundice index between two groups($\bar{x} \pm s$)

Groups	Jaundice resolution time(d)	Jaundice index level($\mu\text{mol/L}$)	
		Before treatment	After treatment
Observation group(n=105)	4.15 $\pm$ 0.82	172.01 $\pm$ 10.85	56.02 $\pm$ 7.36
Control group(n=98)	5.31 $\pm$ 0.92	171.96 $\pm$ 10.79	82.86 $\pm$ 9.32

2.3 两组治疗前后各项胆红素指标水平的比较

两组治疗前间接胆红素、结合胆红素、总胆红素水平比较差异均无统计学意义($P>0.05$)。治疗后,两组间接胆红素、结合

胆红素、总胆红素水平均较治疗前显著降低($P<0.05$),且观察组以上指标水平均显著低于对照组($P<0.05$),见表 3。

表 3 两组治疗前后各项胆红素指标水平的变化比较($\bar{x} \pm s, \mu\text{mol/L}$)

Table 3 Comparison of the Changes of bilirubin indexes between two groups before and after treatment($\bar{x} \pm s, \mu\text{mol/L}$)

Groups	Indirect bilirubin		Conjugated bilirubin		Total bilirubin	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=105)	179.47 $\pm$ 8.78	108.75 $\pm$ 6.21	23.01 $\pm$ 2.43	7.49 $\pm$ 0.85	203.96 $\pm$ 10.12	117.80 $\pm$ 6.52
Control group (n=98)	178.69 $\pm$ 8.75	146.03 $\pm$ 7.32	23.58 $\pm$ 2.50	9.57 $\pm$ 1.02	204.17 $\pm$ 10.30	151.09 $\pm$ 8.34

2.4 两组治疗前后血清 γ -谷氨酰转移酶、胰岛素样生长因子、转铁蛋白水平的对比

治疗前,两组血清 γ -谷氨酰转移酶、胰岛素样生长因子、转铁蛋白水平比较差异均无统计学意义($P>0.05$),治疗后,两组

血清 γ -谷氨酰转移酶、胰岛素样生长因子水平均较治疗前显著降低,转铁蛋白水平较治疗前显著升高,且观察组血清 γ -谷氨酰转移酶、胰岛素样生长因子水平显著低于对照组,转铁蛋白水平明显高于对照组($P<0.05$),见表 4。

表 4 两组治疗前后血清 γ -谷氨酰转移酶、胰岛素样生长因子、转铁蛋白水平的变化比较($\bar{x} \pm s$)

Table 4 Comparison of the the changes of γ -glutamyltransferase, IGF and transferrin levels between two groups before and after treatment($\bar{x} \pm s$)

Groups	γ -GT(U/L)		IGF-1(ng/L)		TRF(g/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group (n=105)	143.89 $\pm$ 17.56	56.01 $\pm$ 6.45	39.63 $\pm$ 5.27	19.30 $\pm$ 2.17	1.35 $\pm$ 0.21	1.96 $\pm$ 0.27
Control group (n=98)	142.90 $\pm$ 17.49	89.56 $\pm$ 10.73	38.79 $\pm$ 5.31	26.78 $\pm$ 3.67	1.36 $\pm$ 0.23	1.60 $\pm$ 0.24

3 讨论

血液胆红素的主要来源是血红蛋白、肠肝循环,由于新生儿的红细胞寿命比较短,肝肠循环是血液胆红素的主要来源,肝肠循环胆红素的水平显著升高使机体中胆红素出现集聚^[8,9]。加上新生儿各器官功能未发育完全,排泄能力较差,代谢相关霉菌不够成熟,使胆红素的排出速度减慢,从而导致新生儿胆红素水平偏高^[10]。临床研究显示^[11]在分娩过程中,窒息、缺氧等因素均会使新生儿胆红素水平升高,虽升高的胆红素具有抗氧化作用,可保护新生儿不受各种氧化物损伤,但过度高胆红素水平会损伤新生儿组织器官,使新生儿出现皮肤、巩膜及黏膜黄染等临床症状^[12]。新生儿黄疸分为生理性和病理性,生理性黄疸是因胆红素代谢特点引起的暂时性黄疸,通常在出生后 2~3 天出现,仅有轻微的食欲不振,无其他临床症状^[13,14]。若新生儿在出生 24h 出现黄疸,每日的血清胆红素升高超过 5 mg/dl 或每小时 >0.5 mg/dl,早产儿持续时间超过 4 周,足产儿

持续时间超过 2 周仍不退,症状出现加深或消退后重复出现则为病理性黄疸^[15]。相关研究显示^[16]生理性黄疸可自行消退,5%~10%的新生儿黄疸是病理性黄疸,需要进行对应的干预治疗。严重的病理性黄疸会引发胆红素脑病,导致急性神经系统功能障碍,若未及时得到有效的治疗,可引起患儿死亡^[17]。蓝光是临床上治疗新生儿黄疸的常用方法,可加速促进胆红素转换及排出,治疗原理在于胆红素吸收一定波长的光线后,将脂溶性 Z 型胆红素转变为水溶性 E 型胆红素,从而降低了胆红素排出的难度^[18,19]。但相关研究表明^[20]由于 E 型胆红素缺乏稳定性,可能会转变为 z 型胆红素,需与其他药物联合治疗保证临床治疗效果。

白蛋白是一类胆红素载体,与 E 型胆红素结合后可提高稳定性,避免转变为 Z 型胆红素^[21]。临床研究表明^[22]白蛋白在机体中具有以下重要的生理功能:维持血浆胶体渗透压的恒定;与体内许多难溶性的小分子有机物和无机离子可逆地结合,形成易溶性的复合物;具有黏性和胶质性,当机体遇到重金属离

子时,会与重金属离子自动结合,具有解毒作用^[23-26]。本研究显示在蓝光照射治疗的基础上,采用白蛋白治疗的患儿黄疸症状及胆红素水平均较治疗前显著降低,提示蓝光联合白蛋白治疗可提高治疗效果。

腺苷蛋氨酸是近年来用于辅助治疗新生儿黄疸的药物,可有效促进黄疸消退,保护肝脏,缓解肝内胆汁淤积^[27]。研究显示^[28]腺苷蛋氨酸活性成分为 S-腺苷-L-蛋氨酸,能够参与体内多种生化反应过程的调控,具有促进胆红素代谢的作用,主要参与体内生物化学反应^[29]。S-腺苷-L-蛋氨酸能够作为甲基和巯基的供体,参与氨基酸代谢过程中的转甲基过程和巯基过程,能够稳定细胞膜结构,减轻受到胆红素的破坏。腺苷蛋氨酸参与体内生物化学反应,尤其是肝脏内能源转化。本研究显示采用联合腺苷蛋氨酸治疗的患儿间接胆红素、结合胆红素、总胆红素水平及治疗疗效均显著优于采用单纯白蛋白治疗的患儿,提示腺苷蛋氨酸可有效改善胆红素代谢,促进黄疸临床症状消退。

血清 TRF 是反映铁代谢的指标,可运载消化道吸收的铁和降解释放红细胞的铁。研究表明 TRF 储量在新生儿体内较少,TRF 水平会随着新生儿黄疸症状的加重而下降,其浓度水平可有效反映新生儿黄疸病情严重程度,通过检测 TRF 水平可鉴别诊断是否由细菌引起。本研究显示采用联合腺苷蛋氨酸治疗的患儿血清 TRF 水平较采用单纯白蛋白治疗的患儿更高,提示腺苷蛋氨酸可有效提高新生儿血清 TRF 水平。

γ -谷氨酰转移酶是一种含巯基的线粒体酶,主要存在于脑肝肾组织中,在多种肝胆系统疾病时升高。当脑组织功能损伤时,细胞膜通透性会增加,导致 γ -谷氨酰转移酶水平升高,因而其可反映脑组织损伤程度。胰岛素样生长因子是一组具有促生长作用的多肽类物质,广泛分布于人体各组织器官中,具有较强的促生长作用,是儿童期的重要生长因子,可有效反映患儿神经毒性损伤程度,评价高胆红素血症的早期脑损伤^[33-35]。在本研究中,两组患儿 γ -谷氨酰转移酶、胰岛素样生长因子水平均显著高于健康新生儿。本研究结果显示采用联合腺苷蛋氨酸治疗的患儿 γ -谷氨酰转移酶、胰岛素样生长因子水平较采用单纯白蛋白治疗的患儿更低,说明了腺苷蛋氨酸联合白蛋白可有效降低 γ -谷氨酰转移酶、胰岛素样生长因子水平,有利于患儿预后。

综上所述,腺苷蛋氨酸联合白蛋白治疗新生儿黄疸的临床疗效显著优于单用白蛋白治疗,其可有效改善患儿的黄疸临床症状,降低血清胆红素、 γ -谷氨酰转移酶、胰岛素样生长因子水平。

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