

半量激素联合他克莫司治疗特发性膜性肾病的临床研究

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摘要 目的:观察半量激素联合他克莫司(FK506)治疗特发性膜性肾病(IMN)的疗效及安全性。方法:采用回顾性研究方法,选取我院经肾活检并结合临床诊断为IMN的患者45例,根据治疗方法不同分为观察组与对照组,观察组给予半量激素联合FK506,对照组给予半量激素联合霉酚酸酯(MMF)。具体用法:泼尼松0.5 mg/(kg·d),清晨顿服,持续2~3个月后逐渐减量,按每10天减10%的药量,减至10 mg/(kg·d)后维持至1年;MMF 750 mg,每日2次;FK506起始用量1 mg,每日2次(服用1周后查谷浓度,血药浓度维持在4~8 ng/ml,根据结果调整用量)。随访时间为1年,观察两组蛋白尿水平、血清白蛋白、总胆固醇、内生肌酐清除率等指标变化。结果:在治疗1个月后,观察组尿蛋白定量明显降低、血清白蛋白明显上升、总胆固醇明显降低,而对照组3个月时才开始出现明显缓解,两组比较差异有统计学意义($P<0.05$);治疗12个月,观察组尿蛋白缓解率达到95.83%,高于对照组的80.95%,两组比较差异有统计学意义($P<0.05$)。两组内生肌酐清除率无明显变化($P>0.05$)。结论:半量激素联合FK506治疗IMN疗效确切。

关键词 激素;他克莫司;特发性膜性肾病

Clinical Study of Half-dose Hormone Combined with Tacrolimus on Idiopathic Membranous Nephropathy

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ABSTRACT OBJECTIVE: To observe the clinical efficacy and safety of half-dose hormone combined with tacrolimus (FK506) on idiopathic membranous nephropathy (IMN). METHODS: By retrospective study, 45 patients with biopsy-proven IMN were collected and divided into observation group and control group. Observation group was given half-dose hormone combined with FK506, and control group was given half-dose hormone combined with mycophenolate mofetil (MMF). The medication was as follows: prednisone 0.5 mg/(kg·d) was taken in the early morning, po, qm, reducing gradually after 2-3 months, and reduced to 10 mg/(kg·d) by 10% every 10 days, maintaining for 1 year; MMF 750 mg was taken twice a day; FK506 was also taken twice a day with initial dose of 1 mg (testing trough concentration after a week, blood concentration maintaining 4-8 ng/ml, drug dosage adjusted according to results). Follow-up time was 1 year. Changes of proteinuria, serum albumin, total cholesterol, endogenous creatinine clearance, were observed in 2 groups. RESULTS: After 1 month of treatment, urine protein quantitative and total cholesterol significantly reduced, while serum protein increased significantly in observation group; the index of control group began to relieve at 3 months; there was statistical significance between 2 groups ($P<0.05$). After 12 months of treatment, remission rate of proteinuria in observation group reached 95.83%, which was higher than 80.95% of control group, there was statistical significance between 2 groups ($P<0.05$). No significant change of endogenous creatinine clearance rate was found in 2 groups ($P>0.05$). CONCLUSIONS: Half-dose hormone combined with FK506 has positive effects on IMN.

KEY WORDS Hormone; Tacrolimus; Idiopathic membranous nephropathy

膜性肾病是以肾小球基底膜上皮细胞下免疫复合物沉积伴肾小球毛细血管基底膜弥漫性增厚为特征的一组疾病,病因未明者称为特发性膜性肾病(IMN)^[1]。目前确切发病机制未明,治疗上循证医学方面尚无确切方案。目前该病的治疗尚无统一有效的治疗方案^[2],一般认为单用激素无效。由于免疫抑制剂的治疗循证医学证据有限,而免疫抑制剂的治疗时机对于膜性肾病的预后至关重要。为此,笔者回顾性研究了本院经肾活检并结合临床确诊IMN患者45例,发现半量激素联合他克莫司(FK506)对于IMN疗效确切,现报道如下。

1 资料与方法

1.1 病例来源

所选45例患者均为我院肾脏内科2009—2012年住院经肾活检确诊为IMN,同时排除膜型狼疮性肾炎、乙肝相关性肾

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炎、肿瘤相关性膜性肾病、药物或毒物引起的膜性肾病。所有患者血压正常,内生肌酐清除率在正常范围内。所有患者资料齐全,定期随访,选用激素及免疫抑制剂治疗前均行知情告知,并签署知情同意书。根据治疗方法不同分为观察组与对照组,两组患者年龄、男女比例、血压水平、蛋白尿水平、肾功能水平等差异均无统计学意义($P>0.05$),见表1。

1.2 治疗方法

观察组患者给予半量激素联合FK506,对照组给予半量激素联合霉酚酸酯(MMF)。具体用法:泼尼松0.5 mg/(kg·d),清晨顿服,持续2~3个月后逐渐减量,按每10天减10%的药量,减至10 mg/(kg·d)后维持至1年;MMF 750 mg,每日2次;FK506起始用法1 mg,每日2次(服用1周后查谷浓度,血药浓度维持在4~8 ng/ml,根据结果调整用量)。

1.3 观察指标

随访时间为1年,观察两组服药治疗1、3、6、12个月的尿蛋白定量、血清白蛋白、总胆固醇、内生肌酐清除率等指标变

表1 两组患者一般情况比较

Tab 1 Comparison of general information between 2 groups

组别	例数	性别		年龄,岁	尿蛋白定量,g/24 h	血清白蛋白,g/L	总胆固醇,mmol/L	内生肌酐清除率,ml/min
		男,例	女,例					
观察组	24	13	11	38.35 ± 12.87	6.48 ± 2.35	20.38 ± 6.52	11.54 ± 1.68	88.13 ± 11.66
对照组	21	11	10	39.15 ± 13.13	6.50 ± 2.29	21.29 ± 5.89	12.03 ± 1.46	89.02 ± 12.12

化,并记录两组治疗过程中出现的不良反应。

1.4 疗效判断标准

完全缓解:尿蛋白定量持续<0.3 g/24 h,血清白蛋白正常,肾功能正常;部分缓解:尿蛋白定量持续>0.3 g/24 h,但下降值超过基础值50%以上,血清白蛋白上升,肾功能无变化;无效:未达到上述标准^[3]。

1.5 统计学方法

采用SPSS 12.0软件包进行统计分析。计数资料比较采用 χ^2 检验,计量资料组间采用 t 检验。 $P<0.05$ 认为差异有统计学意义。

2 结果

2.1 治疗前、后各项指标比较

表2 两组患者治疗前、后各项指标比较($\bar{x} \pm s$)Tab 2 Comparison of indexes between 2 groups before and after treatment($\bar{x} \pm s$)

组别	指标	治疗前	治疗后			
			1个月	3个月	6个月	12个月
观察组	尿蛋白定量,g/24 h	6.48 ± 2.35	2.78 ± 1.21 ^{Δ*}	2.01 ± 0.89 ^{Δ*}	1.01 ± 0.87 ^{Δ*}	0.66 ± 0.12 ^{Δ*}
	血清白蛋白,g/L	20.38 ± 6.52	24.56 ± 6.32 ^{Δ*}	28.56 ± 5.15 ^{Δ*}	30.58 ± 4.23 ^{Δ*}	34.52 ± 4.12 ^{Δ*}
	总胆固醇,mmol/L	11.54 ± 1.68	8.32 ± 1.28 ^{Δ*}	7.83 ± 1.01 ^{Δ*}	6.12 ± 0.97 ^{Δ*}	4.18 ± 1.12 ^{Δ*}
	内生肌酐清除率,ml/min	88.13 ± 11.66	87.85 ± 11.42	87.06 ± 12.18	88.03 ± 11.55	87.92 ± 11.58
对照组	尿蛋白定量,g/24 h	6.50 ± 2.29	4.78 ± 1.97	3.18 ± 1.06 ^Δ	2.50 ± 1.11 ^Δ	1.38 ± 0.86 ^Δ
	血清白蛋白,g/L	21.29 ± 5.89	23.56 ± 4.30	25.56 ± 6.15 ^Δ	30.08 ± 3.15 ^Δ	32.52 ± 3.12 ^Δ
	总胆固醇,mmol/L	12.03 ± 1.46	10.36 ± 1.75	8.83 ± 2.02 ^Δ	6.82 ± 1.37 ^Δ	4.35 ± 0.73 ^Δ
	内生肌酐清除率,ml/min	89.02 ± 12.12	88.85 ± 12.56	88.84 ± 11.12	88.35 ± 11.12	87.01 ± 11.78

与治疗前比较:^Δ $P<0.05$;与对照组比较:^{*} $P<0.05$

vs. before treatment;^Δ $P<0.05$;vs. control group:^{*} $P<0.05$

表3 两组患者疗效比较[例(%)]

Tab 3 Comparison of therapeutic efficacies between 2 groups[case(%)]

组别	例数	完全缓解				部分缓解				无效			
		1个月	3个月	6个月	12个月	1个月	3个月	6个月	12个月	1个月	3个月	6个月	12个月
观察组	24	10(41.67 [*])	12(50.00 [*])	14(58.33 [*])	20(83.33 [*])	8(33.33)	7(29.17)	7(29.17)	3(12.50)	6(25.00)	5(20.83)	3(12.50)	1(4.17)
对照组	21	4(19.05)	6(28.57)	8(38.10)	11(52.38)	5(23.81)	4(19.05)	7(33.33)	6(28.57)	12(57.14)	11(52.38)	6(28.57)	4(19.05)

与对照组比较:^{*} $P<0.05$

vs. control group:^{*} $P<0.05$

2.3 不良反应比较

观察组有1例出现血糖升高,给予调整用量后患者血糖恢复正常;对照组出现腹泻3例,白细胞减少1例。

3 讨论

IMN是成人原发性肾病综合征的常见病理类型,其发病机制未明,目前一般认为是肾小球某些成分如内肽酶、M型磷脂酶A₂受体与其相应的自身抗体结合沉着于上皮细胞下,再激活补体引起的^[1]。

FK506为细胞毒药物,为从真菌中分离出来的具有免疫抑制活性的药物。它是一种神经钙蛋白抑制剂,能干扰钙依赖性信号传导途径,引起钙离子内流,从而使细胞内钙离子浓度增加;启动钙依赖性细胞内转录体系,抑制活化T细胞核因子的去磷酸化,使其不能进入细胞核,达到抑制T细胞增生之目的;还可抑制免疫反应的早期淋巴细胞聚集,并阻止已聚集的淋巴细胞对其他炎症细胞的吸引。这种双重抑制作用使

治疗1个月后,观察组尿蛋白定量明显降低,血清白蛋白明显上升,总胆固醇明显降低,与治疗前比较差异有统计学意义($P<0.05$);治疗3、6、12个月,观察组与上一次比较差异均有统计学意义($P<0.05$);对照组3个月才开始出现明显缓解。随访的1、3、6、12个月,尿蛋白定量、血清白蛋白、总胆固醇两组比较差异均有统计学意义($P<0.05$);内生肌酐清除率两组比较差异均无统计学意义($P>0.05$)。各项指标比较见表2。

2.2 临床疗效比较

观察组在随访的1、3、6、12个月,完全缓解率均高于对照组,差异有统计学意义($P<0.05$),见表3。治疗12个月,观察组尿蛋白缓解率达到95.83%,高于对照组的80.95%,两组比较差异有统计学意义($P<0.05$)。

FK506不仅可用于防止免疫反应的发生,还可用于治疗已发生的免疫反应及自身免疫性疾病^[4]。FK506主要用于治疗和预防器官移植排斥反应,近年来在自身免疫性疾病和肾小球疾病中应用越来越广泛,目前已有随机对照研究,证明其可以有效地治疗IMN^[5]。MMF是一种选择性抑制T淋巴细胞的新型免疫抑制剂,在体内脱脂化后形成具有免疫活性的霉酚酸(MPA),后者抑制次黄嘌呤核苷酸脱氢酶、阻滞鸟嘌呤核苷酸的从头合成途径,进而阻滞DNA和RNA的合成。而嘌呤合成过程对于T、B淋巴细胞的增殖是关键,故MMF可选择性地抑制T、B淋巴细胞。MMF已广泛应用于治疗狼疮性肾炎及难治性肾病综合征,但其治疗IMN疗效临床报道不一致^[6-7]。

本次临床研究显示,在治疗1个月后,观察组尿蛋白定量明显降低、血清白蛋白明显上升、总胆固醇明显降低,而对照组3个月时才开始出现明显缓解,两组比较差异有统计学意义($P<0.05$);治疗12个月,观察组尿蛋白缓解率达到95.83%,

经纤维支气管镜行盐酸氨溴索灌洗治疗支原体肺炎伴肺不张的效果观察

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摘要 目的:观察经纤维支气管镜行盐酸氨溴索灌洗治疗支原体肺炎伴肺不张的疗效。方法:将87例支原体肺炎伴肺不张患儿随机分为常规治疗组($n=41$)、盐酸氨溴索组($n=46$)。2组在常规阿奇霉素治疗的情况下,常规治疗组经纤维支气管镜进行生理盐水灌洗肺不张处,而盐酸氨溴索组予以生理盐水稀释的盐酸氨溴索注射液灌洗。观察两组患儿发热时间及灌洗前后咳嗽次数,并于2周后复查胸部CT,比较两组疗效。结果:两组患儿经纤维支气管镜行灌洗治疗后咳嗽次数均较灌洗前明显减少($P<0.05$),且灌洗后盐酸氨溴索组咳嗽次数为(18.07 ± 4.78)次/d,明显少于常规治疗组灌洗后的(28.07 ± 3.39)次/d($P<0.05$)。盐酸氨溴索组患儿肺不张治疗的总有效率(97.83%)高于常规治疗组(92.68%)($P<0.05$)。但常规治疗组与盐酸氨溴索组的发热时间分别为(5.12 ± 1.22)d、(5.37 ± 2.01)d,差异无显著意义($P>0.05$)。结论:经纤维支气管镜行盐酸氨溴索灌洗治疗支原体肺炎伴肺不张是一种行之有效的临床手段。

关键词 支原体肺炎;肺不张;纤维支气管镜灌洗;盐酸氨溴索

Efficacy Observation of the Treatment of Mycoplasmal Pneumonia Complicating with Pulmonary Atelectasis by Ambroxol hydrochloride Irrigation via Bronchoscopy

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ABSTRACT OBJECTIVE: To observe the therapeutic efficacy of ambroxol hydrochloride irrigation in the treatment of mycoplasmal pneumonia complicating with pulmonary atelectasis via bronchoscopy. METHODS: 87 mycoplasmal pneumonia (MPP) patients with pulmonary atelectasis were randomized into conventional therapy group ($n=41$) and ambroxol hydrochloride group ($n=46$). On the basis of conventional therapy of azithromycin, normal saline (NS) were infused via bronchoscopy in conventional therapy group and irrigation of ambroxol hydrochloride diluted by NS was conducted in ambroxol hydrochloride group. The time of fever and cough times were observed in 2 groups, and the CT were reviewed 2 weeks later. Therapeutic efficacies were compared between 2 groups. RESULTS: The times of cough were decreased significantly in 2 groups after bronchoscopy lavage ($P<0.05$), (18.07 ± 4.78)times/d in ambroxol hydrochloride group which was significantly lower than (28.07 ± 3.39)times/d in conventional treatment group ($P<0.05$). Total effective rate of ambroxol hydrochloride group (97.83%) was higher than that of conventional treatment group (92.68%) ($P<0.05$). The time of fever was (5.12 ± 1.22)d in conventional therapy group and (5.37 ± 2.01)d in ambroxol hydrochloride group, there was no statistical significance ($P>0.05$). CONCLUSIONS: Ambroxol hydrochloride irrigation via bronchoscopy is an effective method for treatment of mycoplasmal pneumonia complicating with pulmonary atelectasis.

KEY WORDS Mycoplasmal pneumonia; Pulmonary atelectasis; Bronchoalveolar lavage; Ambroxol hydrochloride

高于对照组的80.95%,两组比较差异有统计学意义($P<0.05$);内生肌酐清除率方面,两组随访期间差异均无统计学意义($P>0.05$)。不良反应方面,观察组有1例出现血糖升高,给予调整用量后患者血糖恢复正常;对照组出现腹泻3例,白细胞减少1例。

综合本次临床研究结果,笔者认为半量激素联合FK506治疗IMN疗效确切。但由于需要监测血药浓度因而限制了其临床应用,加上缺乏循证医学证据支持,因此,临床上样本量相对偏少。临床上还需要进行多中心大样本研究,且对于患者长期预后,还需要进一步随访观察。

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