

中分子尿毒症毒素及其清除技术的研究进展

刘 旭 张东亮 刘文虎[△]

(首都医科大学附属北京友谊医院肾内科 首都医科大学肾病学系 北京 100050)

摘要 尿毒症毒素是一大组体内代谢的产物,在肾功能衰竭患者体液中水平明显升高,并与尿毒症毒素代谢紊乱或临床表现密切相关。一般认为中分子尿毒症毒素的分子量在 500D-5000D 之间。此类物质蓄积可促进尿毒症性心血管病变的发生发展、抑制机体免疫功能、加重患者营养不良等。研究发现,通过高通量透析、血液透析滤过和血液灌流等方法增加中分子尿毒症毒素的清除,可以为患者带来更好的生活质量和长期生存获益。

关键词 终末期肾病 中分子尿毒症毒素 高通量血液透析 血液透析滤过 血液灌流

中图分类号 R692.5 R459.5 **文献标识码** A **文章编号** 1673-6273(2012)18-3581-03

Progress of Middle Molecular Weight Uremic Toxins and Removal Techniques

LIU Xu, ZHANG Dong-liang, LIU Wen-hu[△]

(Department of Nephrology, Division of Nephrology, Beijing Friendship Hospital, Capital Medical University, 100050, Beijing, China)

ABSTRACT: Uremic toxins are a large group of metabolites, which have significantly higher levels in body fluids of renal failure patients, and are related with toxins metabolic disorders and clinical manifestations closely. It is generally believed that the middle molecular weight uremic toxins are in the interval 500D-5000D. Accumulation of such substances can promote the occurrence of uremic cardiovascular disease development, suppress of immune function, contribute to malnutrition. Researchers found that high-flux dialysis, hemodiafiltration and hemoperfusion and other methods may increase the removal of middle molecular weight uremic toxins, and can bring a better quality of life of patients and long-term survival benefit.

Key words: End stage renal disease; Middle molecular weight uremic toxins; High-flux hemodialysis hemodiafiltration; Hemoperfusion

Chinese Library Classification: R692.5, R459.5 **Document code:** A

Article ID: 1673-6273(2012)18-3581-03

早在 30 年前就有学者发现并提出,中分子物质对于慢性肾脏病(chronic kidney disease,CKD)和终末期肾病(end stage renal disease,ESRD)患者的毒性作用。多种尿毒症症状与此有关。随着这一认识的深入人心,越来越多的临床研究开始关注中分子尿毒症毒素(middle molecular weight uremic toxins),并促进了更高通透性的透析膜和更高对流的透析模式的发展。然而,令人失望的是,这一领域的临床研究尚未发现更好的生物标记指标,用来反映中分子物质的清除情况以及对于患者预后的准确判断。而这也恰恰解释了为何尿素清除指数(Kt/V)虽然预测性并不令人满意,但仍广泛应用于临床^[1]。时过境迁,新近的实验研究再次显示出对中分子毒素的兴趣^[2,3],学者们希望通过各种方法增加这类毒素的清除,从而为血液透析患者带来更多的生存获益^[4]。

1 常见中分子毒素

作者简介 刘旭(1983-),男,医学硕士,住院医师,研究方向:肾脏疾病的诊治与肾脏替代治疗。电话:15210102276,

E-mail: liuxu_000@sina.com

△通讯作者 刘文虎,男,医学博士,主任医师,教授,博士生导师,研究方向:肾脏病的诊治与肾脏替代治疗。电话:010-63139144,

E-mail: liuwh2002@yahoo.cn

(收稿日期 2011-10-24 接受日期 2011-11-20)

1.1 无机磷酸盐

无机磷酸盐和 β₂-微球蛋白一样被认为是较好的反应体内中分子毒素的生物标志,它们都具有较高的体内转移阻力。无机磷酸盐分子量小,并不符合中分子物质的定义。但由于它的物理性质(水合作用、极性等)磷酸盐可模拟中分子物质在透析患者体内的动力学特征^[5]。高磷(酸盐)血症促进了血管钙化,对 CKD 患者来说是不容忽视的心血管风险。然而,能够良好的控制高磷(酸盐)血症并不是一件容易的事。在透析预后与实践研究(Dialysis Outcome and Practice Pattern Study, DOPPS)中发现,52%血液透析患者的血磷水平高于美国肾脏病生存质量指南(Kidney Disease Outcomes Quality Index, K/DOQI)的推荐值,尽管已经广泛使用了磷结合剂^[6]。通过调整透析方案实现控制高磷血症是可能的,增加透析的时间或频率,使用高通量透析和增加对流都是可行的办法。

1.2 β₂-微球蛋白

近几年的研究显示,在长期透析患者当中 β₂-微球蛋白与 β₂-微球蛋白淀粉样变性病的发病密切相关。β₂-微球蛋白血浆浓度与透析患者的死亡率呈正相关。分析 HEMO 研究显示:当血液透析患者的 β₂-微球蛋白血浆浓度超过 27 mg/L 的阈值时,则预期死亡风险将明显增加^[7]。而当浓度处于 42~50 mg/L 时,死亡风险将高出 60%。β₂-微球蛋白的水平可预测透

析患者的死亡率和发生感染的风险^[8]。因此,这一指标应作为评价透析效果的重要参考指标。另外,它具有的二重特性也决定了它的重要意义:一方面, β_2 -微球蛋白可以作为反映中分子毒素的指标用来衡量透析剂量,另一方面,它又是透析系统中的生物不相容标志^[9]。然而,新近又有韩国学者研究发现,在部分维持血液透析的患者中,更高的血清 β_2 -微球蛋白水平带来更好的生存率,反映出在这部分患者中营养状况可能是 β_2 -微球蛋白血清浓度的独立预测因素^[10]。

1.3 蛋白结合毒素

蛋白结合毒素是另一类尿毒症毒素,同样与透析患者的死亡率相关^[11]。甲酚或对甲酚硫酸盐和吡啶酚硫酸盐是该类化合物最主要的成员,它们可以通过诱导氧化应激,引起内皮细胞功能障碍^[12]。此类化合物的结构和代谢动力学都很复杂,因此通过透析将它们清除并不是简单的事。透析清除蛋白结合毒素,目前提出的治疗模式主要有两种:使用蛋白漏出膜或者增加对流清除率。几年前就有学者提出高效对流模式的血液净化方式(血液透析滤过)证实可以维持较低的对甲酚浓度,从而降低了透析患者的死亡率^[13]。然而,最近又有学者提出不同意见:蛋白结合毒素的血液净化与治疗前的血浆浓度有关,且更依赖于弥散清除。对流并不能显著增加这些溶质的清除效果^[14]。

2 对中分子毒素清除的研究

最近的研究认为,高通量透析膜对提高患者生存率有益。两个队列研究提示规律使用高通量透析膜可显著降低血液透析患者的死亡率^[15,16]。分析 HEMO 研究结果提示,使用高通量透析膜大于 3.7 年可降低透析患者死亡率和心血管事件的发生风险^[17]。这一效果并不依赖于尿素 Kt/V,但是与 β_2 -微球蛋白血浆浓度密切相关。在一项前瞻性的随机试验--MPO (Membrane Permeability Outcome)研究中,和进行普通透析对比发现,使用高通量透析膜的患者,无论在糖尿病亚组还是低蛋白血症亚组,都能取得更好的存活率^[18]。

在使用高通量透析时,通过增加对流清除从而获得有益影响的报道在多个研究中被提到。欧洲的 DOPPS 研究指出接受血液透析滤过(HDF)治疗的患者可降低死亡风险^[19]。这种有益的影响经过了多因素分析,包括:年龄、14 种并发症和透析剂量。使用每次透析的液体交换量可推导对流透析剂量。该研究中病例死亡率在低效组(7-15 升)下降 7%,而在高效 HDF 组(15-25 升)则可达 35%,并首次提出增加对流透析剂量可提高患者的生存率。最近又有一项前瞻性研究提示,普通透析患者经过 30 个月血液透析滤过后,成存率可显著改善^[20]。CONTRAST 研究对比接受普通透析和血液透析滤过治疗的患者,并进行评价,发现血磷水平在血液透析滤过组可显著降低,而发生心血管事件的风险与长期生存率的情况仍有待进一步观察^[21]。而血液透析滤过和高通量透析之间的比较,无论在贫血治疗、营养、骨矿代谢,以及血压控制等方面,都未见明显差异。而生存率方面的比较则需要更大规模随机对照研究^[22]。

血液灌流通过吸附剂的吸附作用,也可实现对中分子尿毒症毒素的清除。有研究显示,和普通血液透析相比,血液透析滤

过和血液灌流都可增加尿症患者体内瘦素和神经肽 Y 的清除,从而改善患者的营养状况^[23]。而血液灌流与血液透析滤过的比较,目前尚无较为公认的结论。

3 结语

综上所述,中分子毒素是危害终末期肾病患者长期生存和生活质量的重要角色。无机磷酸盐和 β_2 -微球蛋白代表了两类中分子尿毒症毒素,应结合起来评价透析的充分性。增加溶质对流清除率有益于患者的透析质量。在评价透析效果时应加入血浆 β_2 -微球蛋白等中大分子毒素指标^[24]。

参考文献(References)

- [1] Thomas G, Jaber BL. Convective therapies for removal of middle molecular weight uremic toxins in end-stage renal disease: a review of the evidence[J]. Semin Dial, 2009, 22(6):610-614
- [2] Rhee EP, Souza A, Farrell L, et al. Metabolite profiling identifies markers of uremia[J]. J Am Soc Nephrol, 2010, 21(6):1041-1051
- [3] Kim JC, Garzotto F, Ronco C. Dynamic hemodialysis: a potential solution for middle molecule removal [J]. Contrib Nephrol, 2011, 171: 107-112
- [4] Gondouin B, Hutchison CA. High cut-off dialysis membranes: current uses and future potential [J]. Adv Chronic Kidney Dis, 2011, 18(3): 180-187
- [5] Gura V, Davenport A, Beizai M, et al. Beta2-microglobulin and phosphate clearances using a wearable artificial kidney: a pilot study[J]. Am J Kidney Dis, 2009, 54(1):104-111
- [6] Young EW, Albert JM, Satayathum S, et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study[J]. Kidney Int, 2005, 67(3):1179-1187
- [7] Cheung AK, Rocco MV, Yan G, et al. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study[J]. J Am Soc Nephrol, 2006, 17(2):546-555
- [8] Cheung AK, Greene T, Leypoldt JK, et al. Association between serum 2-microglobulin level and infectious mortality in hemodialysis patients[J]. Clin J Am Soc Nephrol, 2008, 3(1):69-77
- [9] Canaud B, Morena M, Cristol JP, et al. Beta2-microglobulin, a uremic toxin with a double meaning[J]. Kidnet Int, 2006, 69(8):1297-1299
- [10] Kim KM, Kim SS, Kim H, et al. Higher serum beta2-microglobulin levels are associated with better survival in chronic hemodialysis patients: a reverse epidemiology[J]. Clin Nephrol, 2011, 75(5):458-465
- [11] Lin CJ, Wu CJ, Pan CF, et al. Serum protein-bound uraemic toxins and clinical outcomes in haemodialysis patients [J]. Nephrol Dial Transplant, 2010, 25(11):3693-3700
- [12] Tumor Z, Niwa T. Indoxyl sulfate inhibits nitric oxide production and cell viability by inducing oxidative stress in vascular endothelial cells [J]. Am J Nephrol, 2009, 29(6):551-557
- [13] Bammens B, Evenepoel P, Keuleers H, et al. Free serum concentrations of the protein-bound retention solute p-cresol predict mortality in hemodialysis patients[J]. Kidney Int, 2006, 69(6):1081-1087
- [14] Krieter DH, Hackl A, Rodriguez A, et al. Protein-bound uraemic toxin removal in haemodialysis and post- dilution haemodiafiltration [J].

- Nephrol Dial Transplant, 2010, 25(1):212-218
- [15] Chauveau P, Nguyen H, Combe C, et al. Dialyzer membrane permeability and survival in hemodialysis patients [J]. Am J Kidney Dis, 2005, 45(3):565-571
- [16] Krane V, Krieter DH, Olschewski M, et al. Dialyzer membrane characteristics and outcome of patients with type 2 diabetes on maintenance hemodialysis[J]. Am J Kidney Dis, 2007, 49(2):267-275
- [17] Greene T. What did we learn from the HEMO Study? Implications of secondary analyses[J]. Contrib Nephrol, 2005, 149:69-82
- [18] Locatelli F, Martin-Malo A, Hannedouche T, et al. Effect of membrane permeability on survival of hemodialysis patients [J]. J Am Soc Nephrol, 2009, 20(3):645-654
- [19] Canaud B, Bragg-Gresham JL, Marshall MR, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS[J]. Kidney Int, 2006, 69(11):2087-2093
- [20] Panichi V, Rizza GM, Paoletti S, et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies results from the RISCAVID study [J]. Nephrol Dial Transplant, 2008, 23(7):2337-2343
- [21] Penne EL, van der Weerd NC, van den Dorpel MA, et al. Short-term effects of online hemodiafiltration on phosphate control: a result from the randomized controlled Convective Transport Study (CONTRAST) [J]. Am J Kidney Dis, 2010, 55(1):77-87
- [22] Vilar E, Fry AC, Wellsted D, et al. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis [J]. Clin J Am Soc Nephrol, 2009, 4(12):1944-1953
- [23] 宋洁,李辉,张晓东.不同血液净化方式对慢性肾衰患者血清瘦素、神经肽 Y 水平的影响 [J]. 细胞与分子免疫学杂志,2010, 26(11): 1116-1118
- Song J, Li H, Zhang XD. Influence of different blood purification treatment on the serum leptin and neuropeptide Y levels in patients with chronic renal failure [J]. Journal of Cellular and Molecular Immunology. 2010, 26(11):1116-1118(In Chinese)
- [24] Vanholder R, Elout S, Van Biesen W. Do we need new indicators of dialysis adequacy based on middle molecule removal? [J]. Nat Clin Pract Nephrol, 2008, 4(4):174-175
-
- (上接第 3558 页)
- [14] Dincol G, Aktan M, Diz-Kucukkaya R, et al. Treatment of acquired severe aplastic anemia with antilymphocyte globulin, cyclosporin A, methylprednisolone, and granulocyte colony-stimulating factor[J]. Am J Hematol, 2007, 82: 783-786
- [15] Fuhrer M, Rampf U, Baumann I, et al. Immunosuppressive therapy for aplastic anemia in children: a more severe disease predicts better survival[J]. Blood, 2005, 106: 2102-2104
- [16] Bessho M, Hirashima K, Asano S, et al. Treatment of the anemia of aplastic anemia patients with recombinant human erythropoietin in combination with granulocyte colony-stimulating factor: a multicenter randomized controlled study. Multicenter Study Group [J]. Eur J Haematol, 1997, 58: 265-272
- [17] Doney K, Pepe M, Storb R, et al. Immunosuppressive therapy of aplastic anemia: results of a prospective, randomized trial of antithymocyte globulin (ATG), methylprednisolone, and oxymetholone to ATG, very high-dose methylprednisolone, and oxymetholone [J]. Blood, 1992, 79: 2566-2571
- [18] Tichelli A, Schrezenmeier H, Socie G, et al. A randomized controlled study in patients with newly diagnosed severe aplastic anemia receiving antithymocyte globulin (ATG), cyclosporine, with or without G-CSF: a study of the SAA Working Party of the European Group for Blood and Marrow Transplantation[J]. Blood, 2011, 117: 4434-4441
- [19] Zheng Y, Liu Y, Chu Y. Immunosuppressive therapy for acquired severe aplastic anemia (SAA): a prospective comparison of four different regimens[J]. Exp Hematol, 2006, 34: 826-831
- [20] Gluckman E, Rokicka-Milewska R, Hann I, et al. Results and follow-up of a phase III randomized study of recombinant human-granulocyte stimulating factor as support for immunosuppressive therapy in patients with severe aplastic anaemia [J]. Br J Haematol, 2002, 119: 1075-1082