

Intravenous Albumin and Diuretic in Nephrotic Syndrome with Severe Edema: Our Experience and Literature Review

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Abstract

Background and Aim: Steroids are the mainstay of initial treatment in children with Idiopathic Nephrotic Syndrome (INS). The role of diuretics in children with NS is less clear in comparison to adults. In cases with severe or refractory edema, furosemide is often combined with albumin infusion (0.5 to 1 g/kg) to provide symptomatic relief.

Methods: This study was a retrospective chart review of 17 patients with a diagnosis of Steroid Dependent Nephrotic Syndrome (SDNS) admitted for relapse of NS with severe edema who were resistant to diuretic therapy alone. The patients were treated as per unit protocol with an infusion of 100 ml intravenous albumin 20% over 4 hours and 2 doses (one in the morning at 10 AM and the other in the evening at 6 PM) of furosemide 1mg/kg for 3 days. Response to therapy and adverse events were evaluated.

Results: The mean age of the study population was 10.58±1.5 years. All of the patients had severe edema and none of them had responded to intravenous diuretics alone. After co-administration of intravenous albumin infusion and furosemide, the mean weight loss per day per patient was 0.87±0.16 kg.

Conclusion: A significant improvement was noted in all of the patients following co-administration of albumin and furosemide without any adverse events.

Keywords: Nephrotic syndrome; Steroid; Diuretic; Child.

Conflict of interest: The authors declare no conflict of interest.

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Introduction

Nephrotic Syndrome (NS) represents a distinct glomerulopathy with cardinal features of heavy proteinuria, edema, hypoalbuminemia and hyperlipidemia. The characteristic nephrotic range proteinuria is defined as a spot protein/creatinine ratio >2 mg/mg, early morning urine protein of 3+/4+, or urine albumin excretion >40 mg/m² per hour. Idiopathic NS is the most common form of NS in children, responsible for a majority (>90%) of the cases before 10 years of age (1). NS can cause significant complications, thereby leading to increased morbidity and mortality.

It affects the quality of life of children (2,3) Steroids are the mainstay of initial treatment in children with Idiopathic Nephrotic Syndrome (INS). Most (90%) of the children with INS achieve remission within 4 weeks of initiation of steroids. These patients are labelled as Steroid-Sensitive Nephrotic Syndrome (SSNS). About 10% of the cases do not attain remission despite therapy with daily steroids over 4 weeks, who are known as Steroid-Resistant Nephrotic Syndrome (SRNS) (1,4).

Furthermore, Steroid Dependent Nephrotic Syndrome (SDNS) is defined as two consecutive relapses during alternate day steroids or within 14 days of its discontinuation (1). The role of diuretics in children with NS is less clear in comparison to adults. Supportive care with diuretics is often required in children with significant edema as the clinical effects of therapy in the form of diuresis are seen 5 to 10 days after initiation of steroids. In cases with severe or refractory edema, furosemide is often combined with albumin infusion (0.5 to 1 g/kg) to provide symptomatic relief (1). Albumin infusion should be administered cautiously and the patient should be monitored closely for complications like hypertension, volume overload, pulmonary edema and congestive heart failure. (5,6,7) We report our experience with the combined use of intravenous albumin infusion and diuretics in severely edematous patients with SDNS.

Methods

This study was a retrospective chart review of 17 patients with a diagnosis of Steroid Dependent Nephrotic Syndrome (SDNS) admitted for relapse of NS with severe edema. All of the patients had failed to respond to intravenous diuretics (2 doses of furosemide 1 mg/kg) alone. The patients were treated as per unit protocol with 100 ml intravenous albumin 20% as an infusion over 4 hours and 2 doses of furosemide 1 mg/kg for 3 days. Response to therapy and adverse events were evaluated.

Results

The mean age of the study population was 10.58 ± 1.5 years. Laboratory evaluation revealed a mean serum creatinine of 0.74 ± 0.16 mg/dl, mean albumin of 2.37 ± 0.29 mg/dL, and proteinuria of 42.47 ± 2.09 mg/m²/hour. After co-administration of intravenous albumin infusion and furosemide, the mean weight loss per patient per day was 0.87 ± 0.16 kg. None of our patients had any adverse events and there was no evidence of DVT on lower limb Doppler in any of the patients. None of the patients developed AKI at baseline or during the course of hospital stay.

Discussion

Nephrotic syndrome (NS) is a common renal disorder in the pediatric population. Although the majority of the patients respond to treatment with

steroids, attainment of an optimal therapeutic response may take several weeks (8). Various pathophysiologic mechanisms have been suggested for edema formation including underfill and overfill hypotheses. The edema and hypoalbuminemic state that ensues have several clinical consequences ranging from infections to thrombotic events among others. (9-20) Symptomatic treatment plays an important role in this period and assumes an even greater significance in patients who fail to respond to immunosuppressive treatment. Albumin helps protect against intravascular contraction by increasing oncotic pressure and improves the delivery of furosemide to the kidney as a result of increased protein-binding (21). A limited number of studies have evaluated clinical response to a combination of albumin and furosemide for nephrotic syndrome in the pediatric population. Weiss et al. reported weight loss in 24 children with NS treated with albumin and furosemide (22). In a study by Haws et al., combined therapy with diuretics resulted in a mean weight loss of 0.4 kg (1.2% of the body weight) (6). This weight reduction persisted in children whose proteinuria improved, but it was transient in children who continued to have proteinuria. Another prospective study of 14 children with NS also noted a transient decrease in abdominal circumference and body weight (23). Dharmaraj et al. conducted a crossover study and reported increased diuresis and natriuresis with combination therapy compared to the use of diuretics alone (24). In the present study, a substantial drop was noted in the patients' weight after co-administration of furosemide and IV albumin. More importantly, no significant adverse events were observed with this combination in our series. Our experience with a combination of intravenous albumin and a diuretic in severely nephrotic children was quite reassuring. Several studies examining the effect of co-administration of albumin and diuretics on edema in adults with NS have also demonstrated a transient modest clinical benefit; however, definitive recommendations have not been established due to lack of robust evidence (25-29). Moreover, the administration of albumin and diuretics in pediatric patients may produce a more profound increase in the urine output compared to adults, especially in patients with depleted intravascular volumes (24,27). Interestingly, one study found that adding albumin failed to improve diuresis compared to furosemide

alone in adult patients with hypoalbuminemia due to other causes (e.g. cirrhosis with ascites) (30,31). The Indian Academy of Pediatrics (IAP) guidelines recommend administration of albumin 20% (0.5 to 1 g/kg) as an infusion over 2-4 hours together with intravenous furosemide (1 to 2 mg/kg) (1). However, in patients with laboratory evidence of volume expansion (FENa >0.2%), the use of diuretics alone produces diuresis similar to that seen with the use of combined albumin and diuretics in volume contracted patients (20). According to several studies mentioned above, the beneficial effects tend to be transient, and repeat doses are often required. Patients receiving albumin infusions should be closely monitored for respiratory distress, features of fluid overload, congestive heart failure, anaphylaxis, and pulmonary edema (6,7,32).

Conclusion

Controlling edema in patients with nephrotic syndrome is important for symptomatic relief and improved functionality. The use of intravenous albumin infusion in conjunction with diuretics helps to induce diuresis and decrease edema in patients who are refractory to conventional therapy. It is vital to perform a careful evaluation of the volume status of the patient, and certain indices can assist in classifying them as either 'volume contracted' or 'volume expanded'. Albumin should be infused slowly (preferably over 4 hours) to prevent life-threatening complications, and the patients should be closely monitored for adverse events.

Only a handful of studies have evaluated the use of albumin/furosemide for INS-associated edema, and none of them has been specifically conducted on children with SDNS. A significant improvement was noted in all of the patients following co-administration of albumin and furosemide without any adverse events. Large, well-designed studies need to be conducted, especially on patients that are dependent on or resistant to treatment with steroids.

Conflict of Interest

The author declares no conflicts of interest.

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References

1. Bagga A, Ali U, Banerjee S, Kanitkar M, Phadke K D, Senguttuvan P, Sethi S, & Shah, M. Management

- of steroid sensitive nephrotic syndrome: revised guidelines. *Indian pediatrics* 2008;45(3):203–214.
2. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *The Journal of pediatrics* 1981;98(4):561–564. [https://doi.org/10.1016/s0022-3476\(81\)80760-3](https://doi.org/10.1016/s0022-3476(81)80760-3)
3. Minimal change nephrotic syndrome in children: deaths during the first 5 to 15 years' observation. Report of the International Study of Kidney Disease in Children. *Pediatrics* 1984;73(4):497–501.
4. Tarshish P, Tobin JN, Bernstein J, Edelmann C M, Jr. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. *Journal of the American Society of Nephrology: JASN* 1997;8(5):769–776.
5. Cadnapaphornchai MA, Tkachenko O, Shchekochikhin D, & Schrier RW. The nephrotic syndrome: pathogenesis and treatment of edema formation and secondary complications. *Pediatric nephrology* 2014;29(7):1159–1167. <https://doi.org/10.1007/s00467-013-2567-8>
6. Haws RM, Baum M. Efficacy of albumin and diuretic therapy in children with nephrotic syndrome. *Pediatrics* 1993;91(6):1142–1146.
7. Reid C J, Marsh M J, Murdoch IM, Clark G. Nephrotic syndrome in childhood complicated by life threatening pulmonary edema. *BMJ (Clinical research)* 1996; 312(7022):36–38. <https://doi.org/10.1136/bmj.312.7022.36>
8. McCaffrey J, Lennon R, Webb N J. The non-immunosuppressive management of childhood nephrotic syndrome. *Pediatric nephrology* 2016;31(9):1383–1402. <https://doi.org/10.1007/s00467-015-3241-0>
9. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, et al. Management of childhood onset nephrotic syndrome. *Pediatrics* 2009; 124(2):747–757. <https://doi.org/10.1542/peds.2008-1559>
10. Willemsen RH, Delgado-Carballar V, Elleri D, Thankamony A, Burke GA, Nicholson JC, et al. Tolvaptan use during hyperhydration in pediatric intracranial lymphoma with SIADH. *Endocrinology, diabetes & metabolism case reports* 2016;16-66. <https://doi.org/10.1530/EDM-16-0066>
11. Vande Walle J, Donckerwolcke R, Boer P, van Isselt, HW, Koomans HA, Joles JA. Blood volume, colloid osmotic pressure and F-cell ratio in children with the nephrotic syndrome. *Kidney international* 1996; 49(5):1471–1477. <https://doi.org/10.1038/ki.1996.207>
12. Geers AB, Koomans HA, Boer P, Dorhout Mees EJ. Plasma and blood volumes in patients with the nephrotic syndrome. *Nephron* 1984;38(3):170–173. <https://doi.org/10.1159/000183302>
13. Epstein AA. Concerning the causation of edema in chronic parenchymatous nephritis; method for its alleviation. *The American journal of medicine* 1952;

- 13(5):556–561. [https://doi.org/10.1016/0002-9343\(52\)90020-x](https://doi.org/10.1016/0002-9343(52)90020-x)
14. Humphreys MH. Mechanisms and management of nephrotic edema. *Kidney international* 1994; 45(1), 266–281. <https://doi.org/10.1038/ki.1994.33>
 15. Meltzer J I, Keim H J, Laragh J H, Sealey J , Jan K M, Chien S. Nephrotic syndrome: vasoconstriction and hypervolemic types indicated by renin-sodium profiling. *Annals of internal medicine* 1979;91(5), 688–696. <https://doi.org/10.7326/0003-4819-91-5-688>
 16. Palmer B F, Alpern R J. Pathogenesis of edema formation in the nephrotic syndrome. *Kidney international*. 1997;59:S21–S27.
 17. Dorhout Mees E J, Koomans H A. Understanding the nephrotic syndrome: what's new in a decade? *Nephron* 1995;70(1): 1–10. <https://doi.org/10.1159/000188535>
 18. Schrier R W, Fassett R G. A critique of the overfill hypothesis of sodium and water retention in the nephrotic syndrome. *Kidney international* 1998; 53(5):1111–1117. <https://doi.org/10.1046/j.1523-1755.1998.00864.x>
 19. Vande Walle JG, Donckerwolcke RA, van Isselt J W, Derckx FH, Joles JA, Koomans HA. Volume regulation in children with early relapse of minimal-change nephrosis with or without hypovolemic symptoms. *Lancet* 1995;346:148–152. [https://doi.org/10.1016/s0140-6736\(95\)91210-x](https://doi.org/10.1016/s0140-6736(95)91210-x)
 20. Kapur G, Valentini RP, Imam AA, Mattoo TK. Treatment of severe edema in children with nephrotic syndrome with diuretics alone--a prospective study. *Clinical journal of the American Society of Nephrology: CJASN* 2009;4(5):907–913. <https://doi.org/10.2215/CJN.04390808>
 21. Inoue M, Okajima K, Itoh K, Ando Y, Watanabe N, Yasaka T, et al. Mechanism of furosemide resistance in analbuminemic rats and hypoalbuminemic patients. *Kidney international* 1987;32(2):198–203. <https://doi.org/10.1038/ki.1987.192>
 22. Weiss RA, Schoeneman M, Greifer I. Treatment of severe nephrotic edema with albumin and furosemide. *New York state journal of medicine* 1984;84(8):384–386.
 23. Bircan Z, Kervancıoğlu M, Katar S, Vitrinel A. Does albumin and furosemide therapy affect plasma volume in nephrotic children? *Pediatric nephrology* 2001;16(6):497–499. <https://doi.org/10.1007/s004670100576>
 24. Dharmaraj R, Hari P, Bagga A. Randomized cross-over trial comparing albumin and furosemide infusions in nephrotic syndrome. *Pediatric nephrology* 2009; 24(4):775–782. <https://doi.org/10.1007/s00467-008-1062-0>
 25. Na KY, Han JS, Kim YS, Ahn C, Kim S, Lee JS, et al. Does albumin preinfusion potentiate diuretic action of furosemide in patients with nephrotic syndrome? *Journal of Korean medical science* 2001; 16(4):448–454. <https://doi.org/10.3346/jkms.2001.16.4.448>
 26. Sjöström PA, Odlin BG, Beermann BA, Karlberg BE. Pharmacokinetics and effects of furosemide in patients with the nephrotic syndrome. *European journal of clinical pharmacology* 1989;37(2):173–180. <https://doi.org/10.1007/BF00558227>
 27. Fliser D, Zurbrüggen I, Mutschler E, Bischoff I, Nussberger J, Franek E, et al. Coadministration of albumin and furosemide in patients with the nephrotic syndrome. *Kidney international* 1999;55(2):629–634. <https://doi.org/10.1046/j.1523-1755.1999.00298.x>
 28. Ghafari A, Mehdizadeh A, Alavi-Darazam I, Rahimi E, Kargar C, Sepehrvand N. Co-administration of albumin-furosemide in patients with the nephrotic syndrome. *Saudi journal of kidney diseases and transplantation: an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia* 2001;22(3):471–475.
 29. Ho JJ, Adnan AS, Kueh YC, Ambak NJ, Van Rostenberghe H, Jummaat F. Human albumin infusion for treating edema in people with nephrotic syndrome. *The Cochrane database of systematic reviews* 2019;7(7):CD009692. Advance online publication. <https://doi.org/10.1002/14651858.CD009692.pub2>
 30. Chalasani N, Gorski JC, Horlander JC, Sr Craven R, Hoen H, Maya J, et al. Effects of albumin/furosemide mixtures on responses to furosemide in hypoalbuminemic patients. *Journal of the American Society of Nephrology: JASN* 2001;12(5):1010–1016.
 31. Kitsios GD, Mascari P, Ettunsi R, & Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *Journal of critical care* 2014;29(2):253–259. <https://doi.org/10.1016/j.jcrc.2013.10.004>
 32. Liunbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossettias G. Italian Society of Transfusion Medicine and Immunohematology (SIMITI). Recommendations for the use of albumin and immunoglobulins. *Blood transfusion, Transfusion del sangue* 2009;7(3):216–234. <https://doi.org/10.2450/2009.0094-09>