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Phlebotomy improves kidney function in pediatric cyanotic nephropathy: A case report

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ABSTRACT

Children with cyanotic congenital heart diseases (CCHDs) have several risk factors for the development of several complications, including cyanotic nephropathy (CN). However, due to poor awareness of this problem, CN occasionally progresses to chronic kidney disease (CKD). In the long term, kidney cells subjected to chronic hypoxia undergo further damage, which increases the risk of developing end-stage kidney disease. There are no standardized therapeutic approaches for these cases, especially for children, although phlebotomy is an option. Our case demonstrates a 12-year-old boy with an inoperable, complex CCHD and persistent proteinuria with decreased kidney function. After receiving consecutive treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker, the proteinuria did not resolve, and the kidney function deteriorated. Phlebotomy was performed to treat the proteinuria, and the kidney function improved. Within the three months following the first phlebotomy procedure, the patient was less cyanotic and had improved hemodynamic stability. Proteinuria reduction and improvement of estimated glomerular filtration rate were noted; however, the proteinuria gradually worsened after three months. In conclusion, phlebotomy might delay CKD progression in children with CN due to inoperable, complex CCHD. The positive effects in our case were temporary; therefore, repeated therapeutic phlebotomies should be considered.

Implication for health policy/practice/research/medical education:

Children with cyanotic congenital heart diseases are at risk of developing cyanotic nephropathy; thus, serious problems such as end-stage kidney disease could occur. Phlebotomy, as an alternative treatment should be considered as a therapeutic option in severe non-operable children with proteinuria.

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Introduction

Cyanotic nephropathy (CN) involves significant morphological and functional changes in the kidneys due to undertreated cyanotic congenital heart disease (CCHD) (1). Late surgical treatment secondary to delayed diagnosis of CCHD contributes significantly to adverse outcomes, including CN, especially in developing countries (2). This is especially true for island countries, such as Indonesia,

that have inequalities in access to healthcare and a lack of pediatric cardiologists (3). A prospective cohort study in Yogyakarta, Indonesia, confirmed that CCHDs were more likely to be initially misdiagnosed, with delayed diagnosis in 86.2% of cases (4). If left untreated, CCHDs can progress to progressive chronic kidney disease (CKD). The mortality rate among children with CN is 51% (1); however, in Indonesia, the incidence of CN in children

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remains underreported.

Adequate interventions are needed to improve survival and quality of life in children with CN due to CCHD. However, no standardized therapeutic approaches exist for these cases, especially for children. Phlebotomy, a procedure commonly indicated for treating polycythemia vera (PV), has increased interest in investigating whether decreasing blood viscosity might benefit CCHD patients (5). Previously, this procedure produced favorable outcomes in adult CCHD patients developing secondary CN (6,7). However, its efficacy and safety in children have not yet been investigated. Herein, we report a case of a child with CN secondary to CCHD that improved with phlebotomy.

Case Presentation

A 12-year-old-boy with complex CCHD was referred to the paediatric nephrology clinic at Dr. Cipto Mangunkusumo general hospital (CMGH), a national referral hospital in Jakarta, Indonesia, due to persistent proteinuria and decreased estimated glomerular filtration rate (eGFR). At 10 years of age, he was initially referred to the Paediatric cardiology clinic from a rural area 354 kilometres northwest of our centre due to cyanosis since 2 months of age and poor growth, with a body weight of 22 kg (<1st percentile, CDC-NCHS 2000 growth chart) and height of 118 cm (<1st percentile, CDC-NCHS 2000 growth chart). He was diagnosed with pulmonary atresia (PA), ventricular septal defect (VSD), and major aortopulmonary collateral arteries (MAPCAs). The cardiology team concluded that the case was inoperable, and the patient was treated conservatively with an angiotensin-converting enzyme inhibitor (ACEI) and diuretics.

After three years of treatment, the patient developed persistent proteinuria (urine protein 2+ on a dipstick test) for 15 months. He was hemodynamically stable, with a blood pressure of 118/63 mm Hg (95th percentile) (8). He was cyanotic with nephrotic range proteinuria (24-hour proteinuria ≥ 40 mg/m²/h); however, no edema or haematuria was noted. His lipid profile revealed a total cholesterol of 184 mg/dL, high-density lipoprotein of 35 mg/dL, elevated low-density lipoprotein of 132 mg/dL, and elevated plasma triglyceride level of 180 mg/dL. His baseline laboratory results are shown in Table 1.

Further investigations to rule out possible immunological causes, including C3, C4, and antistreptolysin O titer, were normal. Infection screening, including human

immunodeficiency virus (HIV), hepatitis B, and hepatitis C, was also negative. Abdominal ultrasound revealed a marked decrease in kidney size, with a right kidney length of 6.13 cm (<2.5th percentile) and a left kidney length of 4.32 cm (<2.5th percentile) (9). The patient was diagnosed with CN and treated consecutively with 0.25 mg/kg/d lisinopril, which was switched to 3.6 mg/kg/d valsartan. However, the proteinuria did not resolve.

The patient was referred to a pediatric hematologist for phlebotomy. The volume of blood drawn was 215 mL, which was estimated using the following formula: (initial hematocrit [%] – desired hematocrit [%])/3 \times body weight [kg] \times 4. The desired hematocrit level was 52%. Replacement fluid was not administered as the patient tolerated the blood loss well. No side effects of phlebotomy were reported.

Cyanotic and kidney function parameters improved during the first 3 months following phlebotomy; however, these parameters gradually worsened in subsequent months (Table 1). No signs of infection or medication changes were recorded. Despite compliance with the treatment, the patient's kidney function worsened. Therefore, another phlebotomy was planned but could not be performed due to COVID-19-related restriction policies.

Discussion

In the present case, phlebotomy was effective in reducing proteinuria in a pediatric CCHD patient with polycythemia. The risk of developing CN increases significantly among children whose cyanosis is untreated for more than 10 years (1). Two mechanisms have been proposed to contribute to proteinuria in children with CCHD. First, kidney dysfunction is preceded by heart failure (cardiorenal syndrome type 2) (6). Triggers include chronic increases in kidney venous pressure, chronic oxidative stress, and pro-inflammatory signaling, all of which reduce glomerular plasma flow and eGFR (10). Furthermore, hyper-viscosity secondary to polycythemia causes shear stress due to the high number of erythrocytes passing across the capillary unit. Consequently, the peritubular capillary blood flow decreases, which induces hypoxia and later produces a nitric oxide-mediated angiogenic increase in the capillary beds, which increases the glomerular capillary pressure. Progression leads to hypertrophied podocytes and glomerulomegaly due to endothelial proliferation, which subsequently leads to

Table 1. Pre- and post-phlebotomy laboratory results

Parameters	Reference Value	Baseline	Month(s) after procedure			
			1	3	12	15
eGFR (mL/min/1.73 m ²)	≥ 90	72	81.2	84	73.8	60
24-hour proteinuria (mg/m ² /h)	<40	42	10.8	52.1	60.2	77
Hct (%)	40–51	60	55.8	57	58	N/A

Abbreviations: eGFR; Estimated glomerular filtration rate, Hct; Haematocrit, N/A; Not available.

decreased kidney filtration fraction and proteinuria (6,11).

In the second mechanism, kidney dysfunction involves a proximal tubular lesion, which is more prominent during infancy and early childhood, especially in patients with severe cyanosis. Levels of N-acetyl- β -D-glucosaminidase (NAG) and α 1-microglobulin (α 1-MG) protein in the urine support this finding. NAG indicates ongoing tubular cellular damage, while α 1-MG is almost completely reabsorbed by the proximal tubule under physiological conditions (12).

Renal-angiotensin-aldosterone system (RAAS) inhibitors, such as ACEIs and angiotensin II receptor blockers (ARBs), have generally been used. However, these medications may not be well-tolerated in some patients. This was observed in our case, in which ACEI and ARB administration failed to resolve the proteinuria. A recent study has reported no additional effects of dual RAAS blockade on reducing all-cause mortality (13).

To our knowledge, this case was the first phlebotomy performed in our country to treat CN in a child. Although not commonly used, phlebotomy is a promising option that leads to stabilization in CN patients. A study revealed that phlebotomy produced beneficial effects on kidney function by decreasing the hematocrit level, thereby reducing blood viscosity (7). This observation was in line with our findings of reduced proteinuria and hematocrit and improved eGFR in the present case.

Polycythaemia in patients with CCHD is different from primary erythrocytosis of PV. In adults, the current clinical practice targets are a hematocrit below 65% after phlebotomy for patients with CCHD (14). However, guidelines on phlebotomy in children with CCHD have not yet been established. Calculating the maximum allowable intraprocedural blood loss is advisable: (estimated blood volume \times [initial hematocrit – desired hematocrit] / initial hematocrit) (15). The blood volume drawn from our patient was within the tolerable range and did not produce signs of hypovolemia. In some cases, adequate volume replacement is needed to prevent a sudden decrease in systemic blood flow following blood loss. It is commonly prescribed for patients who cannot tolerate rapid plasma loss, especially those with a hemoglobin level below 11 g/dL and symptoms of fainting, pallor, or sweating (5).

Several reports have described the effectiveness of phlebotomy in improving kidney function in adult patients with CN. A 55-year-old female with operated PA-VSD developed persistent proteinuria, with a hemoglobin level of 18 g/dL and creatinine level of 2.4 mg/dL. After a series of three phlebotomies, her hemoglobin level decreased to 14.9 g/dL and was accompanied by a decrease in creatinine to 1.8 g/dL. In addition, the urine protein-to-creatinine ratio decreased by 57%. Repeated phlebotomies were scheduled at each outpatient visit, and the patient's kidney function was stabilized (7). Comparable results were observed in a 49-year-old male with operated tricuspid atresia. He had an initial hemoglobin count of

23.8 g/dL and a hematocrit level of 80.8%. Due to severe polycythemia, he underwent periodic phlebotomies that resulted in stable renal function (6).

To date, no studies have investigated the efficacy of phlebotomy in children. Our findings suggest that this procedure might be a promising option to improve important clinical and laboratory outcomes in children with CN. However, the positive effects of phlebotomy in our case persisted for only three months and were followed by proteinuria and worsening of the eGFR and hematocrit. Therefore, the implementation of periodic phlebotomies should be considered for future cases.

Conclusion

In children with inoperable complex CCHD and developing CN, phlebotomy might delay the progression to CKD. The positive effects of phlebotomy in our case were temporary; therefore, we recommend that therapeutic phlebotomies be repeated when the proteinuria increases to a nephrotic range.

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Authors' contribution

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Conflicts of interest

The authors declare that they have no competing interests.

Disclosure

Parts of this study were presented as a poster at the 14th Asian Congress of Pediatric Nephrology, Taipei, Taiwan, 2021.

Data availability statement

All data generated during this study are presented in this article. Further enquiries can be requested to the corresponding author.

Ethical issues

This case report was conducted in accord with the World Medical Association Declaration of Helsinki. The parent of the patient has given us a written informed consent for publication as a case report. Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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References

1. Naik VS, Phadke VD, Kanhere SV. Nephropathy in a child suffering from tetralogy of Fallot. *IJCR*. 2020;6:312–3. doi: 10.32677/IJCR.2020.v06.i06.009.
2. Liu Y, Chen S, Zühlke L, Babu-Narayan SV, Black GC, Choy MK, et al. Global prevalence of congenital heart disease in school-age children: a meta-analysis and systematic review. *BMC Cardiovasc Disord*. 2020 Nov 19;20:488. doi: 10.1186/s12872-020-01781-x.
3. Palupi-Baroto R, Hermawan K, Murni IK, Nurlitasari T, Prihastuti Y, Sekali DRK, et al. High fibroblast growth factor 23 as a biomarker for severe cardiac impairment in children with chronic kidney disease: a Single Tertiary Center Study. *Int J Nephrol Renovasc Dis*. 2021 Jun 8;14:165-171. doi: 10.2147/IJNRD.S304143.
4. Murni IK, Wirawan MT, Patmasari L, Sativa ER, Arafuri N, Nugroho S, et al. Delayed diagnosis in children with congenital heart disease: a mixed-method study. *BMC Pediatr*. 2021 Apr 21;21:191. doi: 10.1186/s12887-021-02667-3.
5. Kim KH, Oh KY. Clinical applications of therapeutic phlebotomy. *J Blood Med*. 2016 Jul 18;7:139-44. doi: 10.2147/JBM.S108479.
6. Ortega-Díaz M, Puerta Carretero M, Corchete E, Martín Navarro JA, Jaldo MT, Albalade M, et al. A case report of cyanotic nephropathy. *Nefrologia (Engl Ed)*. 2019;39:96-98. English, Spanish. doi: 10.1016/j.nefro.2018.05.001.
7. Omonuwa KO, Talwar A, Dedopoulos S, Mailloux LU. Repeated phlebotomies improve and stabilise renal function in cyanotic nephropathy. *BMJ Case Rep*. 2009;2009:bcr10.2008.1084. doi: 10.1136/bcr.10.2008.1084.
8. Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics*. 2017;140:e20171904. doi: 10.1542/peds.2017-1904.
9. Obrycki Ł, Sarnecki J, Lichosik M, Sopińska M, Placzyńska M, Stańczyk M, et al. Kidney length normative values in children aged 0-19 years - a multicenter study. *Pediatr Nephrol*. 2022;37:1075-1085. doi: 10.1007/s00467-021-05303-5. PMID: 34657197; PMCID: PMC9023417.
10. Cruz DN, Schmidt-Ott KM, Vescovo G, House AA, Kellum JA, Ronco C, et al. Pathophysiology of cardiorenal syndrome type 2 in stable chronic heart failure: workgroup statements from the eleventh consensus conference of the Acute Dialysis Quality Initiative (ADQI). *Contrib Nephrol*. 2013;182:117-36. doi: 10.1159/000349968.
11. Gupte PA, Vaideeswar P, Kandalkar BM. Cyanotic nephropathy--a morphometric analysis. *Congenit Heart Dis*. 2014;9:280-5. doi: 10.1111/chd.12121.
12. Zheng J, Yao Y, Han L, Xiao Y. Renal function and injury in infants and young children with congenital heart disease. *Pediatr Nephrol*. 2013;28:99-104. doi: 10.1007/s00467-012-2292-8.
13. Loutradis C, Price A, Ferro CJ, Sarafidis P. Renin-angiotensin system blockade in patients with chronic kidney disease: benefits, problems in everyday clinical use, and open questions for advanced renal dysfunction. *J Hum Hypertens*. 2021;35:499-509. doi: 10.1038/s41371-021-00504-9.
14. Mithoowani S, Laureano M, Crowther MA, Hillis CM. Investigation and management of erythrocytosis. *CMAJ*. 2020 Aug 10;192:E913-E918. doi: 10.1503/cmaj.191587.
15. Nemergut ME, Haile DT, Mauermann WJ, Flick RP. Chapter 20: Blood conservation and transfusion medicine. In: Davis PJ, Cladis FP, editors. *Smith's anesthesia for infants and children*. 9th edition. St. Louis, Missouri: Elsevier; 2017:399–422. doi: 10.1016/B978-0-323-34125-7.00020-6.

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