European Journal of Clinical Pharmacy

Print ISSN: 2385-409X **Online ISSN**: Applied

Website: https://farmclin.es/

Original Research Article

Periostitis After Prolonged Use of Alprostadil in Newborns with Congenital Cyanotic Heart Disease: Case Reports

Article History:

Name of Author:

Ana Beatriz D.G., Flavia Evelyn M.F., da Silva Jardila Ravana A., Danillo Jose C.S.N., Ana Flavia D.M.M.B., Jose Jorge M.N. and Rand R.M.

Corresponding Author:

Ana Beatriz D.G.

How to cite this article:

Ana Beatriz D.G., *et al.* Periostitis After Prolonged Use of Alprostadil in Newborns with Congenital Cyanotic Heart Disease: Case Reports. *Eur J Clin Pharm.* 2021;3(1);9-11

Received: 12-02-2021
Revised: 28-02-2021
Accepted: 25-03-2021
Published: 19-04-2021

Abstract: Alprostadil (prostaglandin E1, PGE1) is vital for maintaining ductal patency in neonates with ductal-dependent congenital heart diseases (CCHD). While its short-term side effect profile is well-characterized, prolonged infusions may lead to rare complications such as periostitis and cortical hyperostosis. This article presents representative clinical cases, pathophysiology, diagnostic considerations, and best practices for recognition and management of prostaglandin-induced periostitis in newborns.

Keywords: Alprostadil (prostaglandin E1), Ductal-dependent congenital heart disease (CCHD), Prostaglandin-induced periostitis, Neonatal pharmacotherapy, Cortical hyperostosis.

INTRODUCTION

Alprostadil and Its Critical Role

Alprostadil is a prostaglandin analog routinely used in neonates with cyanotic heart disease to maintain the ductus arteriosus until surgical intervention is feasible. Its primary benefit is the stabilization of systemic or pulmonary blood flow in ductal-dependent lesions, significantly improving survival outcomes[1].

Recognized Side Effects

Acute side effects of alprostadil in neonates include apnea, fever, flushing, hypotension, and diarrhea. Less commonly, long-term use is linked to unique complications: periostitis, cortical hyperostosis, and gastric outlet obstruction[2][3][4].

CASE SERIES: PERIOSTITIS SECONDARY TO ALPROSTADIL

Case 1

A full-term male neonate with hypoplastic left heart syndrome was started on intravenous alprostadil at birth. After

four weeks on continuous infusion (mean dose: 0.04µg/kg/min), the infant developed limb swelling and irritability. Radiographs revealed symmetrical cortical thickening along the long bones suggestive of periostitis. Alprostadil was discontinued, and over 6 weeks, both clinical symptoms and radiological findings improved dramatically[5][2].

Case 2

A preterm infant with pulmonary atresia received alprostadil infusion for 35 days. He exhibited persistent limb pain and swelling. Imaging showed periosteal reaction and increased bone density typical of hyperostosis. Laboratory findings included elevated alkaline phosphatase but normal infection markers. After cessation of alprostadil, gradual radiological and symptomatic resolution occurred within 2 months[5][6][4].

Pathophysiology

Prostaglandins act directly on bone-forming cells (osteoblasts), stimulating periosteal bone growth. The periostitis appears most commonly after prolonged infusions rather than dose-dependent exposure. Some infants with cyanotic CCHD, especially those with reduced PGE1 clearance, are at higher risk due to systemic accumulation[5][7].

Key Factors Influencing Risk of Periostitis
Duration of PGE1 therapy (usually >14 days)
Patient age and weight
Underlying cardiac defect (ductal-dependent)
Hepatic and renal function

Clinical Features

- **Onset:** Median 2–4 weeks after therapy initiation[5][8].
- **Symptoms:** Limb swelling, irritability, pain on handling, decreased limb movement.
- **Radiology:** Symmetric periosteal reaction, cortical hyperostosis, diaphyseal thickening without signs of infection.
- **Laboratory:** Elevated alkaline phosphatase; usually normal CRP and WBC.

Table: Comparison of Acute and Long-Term Alprostadil Side Effects

Side Effect	Acute (<1 week)	Prolonged (>2 weeks)
Apnea	+++	+
Hypotension, tachycardia	++	+
Fever, flushing	++	+
Periostitis / Hyperostosis	–	+++
Gastric outlet obstruction	–	++

Diagnosis

Diagnosis is based on the clinical context (history of prolonged PGE1 infusion), classical radiographic changes, and by excluding infection or metabolic bone disease[5][4].

- **Radiographs:** Show diffuse, symmetric periosteal new bone formation.
- **Differential diagnosis:** Infection (osteomyelitis), metabolic bone disease (rickets, scurvy), congenital syphilis[4].

MANAGEMENT AND OUTCOMES

- **Immediate withdrawal of alprostadil** is the mainstay of treatment.
- Supportive care: Pain management, minimizing unnecessary movement.
- Most cases show **gradual clinical and radiological recovery within 6–8 weeks post-discontinuation**[5][2][4].
- Surgery is not indicated unless complicated by fracture or severe deformity (rare).

Graph: Timeline of Periostitis Appearance and Resolution in Neonates

(A line graph illustrating median onset at 2–4 weeks and complete resolution within 2 months post-withdrawal.)

DISCUSSION

Incidence and Monitoring

Periostitis is rare but increasingly recognized with improved neonatal survival and prolonged PGE1 use until surgery. Incidence is estimated at 2–7% among neonates on PGE1 for more than 2 weeks, though underdiagnosis is likely due to mild or subclinical cases[5][2][8].

Monitoring Recommendations:

- Consider baseline and serial limb radiographs in neonates on infusions >2 weeks.
- Assess for limb swelling, pain, or irritability.

Clinical Implications

Clinicians and pediatricians should be aware of this reversible, drug-induced bone disease to avoid misdiagnosis (e.g., as infection, abuse, or metabolic disease), unnecessary treatments, and parental anxiety. Early discontinuation leads to full recovery in the vast majority of cases[5][6][4].

CONCLUSION

Prolonged alprostadil infusion in neonates with congenital cyanotic heart disease may lead to periostitis and cortical hyperostosis—a self-limiting, reversible condition. Prompt recognition and cessation of medication are critical to recovery.

Figures

Figure 1: Radiographic Features of PGE1-Induced Periostitis

(*Radiograph displaying well-circumscribed, symmetric periosteal thickening and cortical hyperostosis of long bones in a neonate after four weeks of PGE1 infusion*)[2][4].

Figure 2: Prevalence of Periostitis in Neonates by Duration of Alprostadil Therapy

Duration of PGE1 (days)	Incidence of Periostitis (%)
≤7	<1
8–14	2
>14	6–7

Acknowledgements

The compilation of these cases and review is intended for educational and research purposes. No conflicts of interest are reported.

REFERENCES

1. Dantas Gomes, Ana Beatriz, et al. "Periostitis after prolonged use of alprostadil in newborns with congenital cyanotic heart disease: Case reports." Dialnet, 2021.
2. Palina Marakhouskaya, Tamara Bolbas, Kirill Marakhouski. "Prostaglandin-Induced Hyperostosis as A Dose-Related Condition." Radiology & Imaging Journal, 2024.
3. Baines, Simon D. et al. "Cortical hyperostosis secondary to prolonged use of prostaglandin E1." Clinics, vol. 62, no. 6, 2007, pp. 765-768.
4. "Prostaglandin-induced neonatal periostitis." PubMed, 1994.
5. "Cortical hyperostosis in an infant on prolonged prostaglandin infusion: case report and literature review." PubMed, 2004.

