Research Article ISSN 2835-3587

Radiology & Imaging Journal

Prostaglandin-Induced Hyperostosis as A Dose-Related Condition

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Received: 08 Aug 2024; **Accepted:** 17 Sep 2024; **Published:** 25 Sep 2024

Citation: Palina Marakhouskaya, Tamara Bolbas, Kirill Marakhouski. Prostaglandin-Induced Hyperostosis as A Dose-Related Condition. Radiol Imaging J. 2024; 3(3): 1-4.

ABSTRACT

Background: *Prostaglandin-induced hyperostosis is caused by prolonged infusion of prostaglandin E (PGE). It commonly involves diaphysis of the long bones of the upper and lower limbs, clavicles, ribs, and scapulae. PGE therapy is commonly used to maintain the patency of ductus arteriosus in neonates with ductal-dependent congenital heart defects (CHDs). Reversible cortical hyperostosis of long bones is a side-effect of PGE injections. Some studies suggested that periostitis was more dependent on duration than on dosage of the prostaglandins administered. However, infants with cyanotic CHD, which causes decreased pulmonary blood flow and reduced PGE clearance, may have higher systemic concentration of PGE.*

Aim: *To determine the minimal injected dose of PGE for risk of developing prostaglandin-induced periostitis in infants with ductal-dependent CHD.*

Methods: *Forty-eight infants with ductal-dependent CHDs and previous preoperative PGE infusion (> 2 d) who underwent reconstructive cardiac surgery were retrospectively included and separated into two groups. The study group included 20 patients (6 females) meeting the inclusion criteria of PGE-induced hyperostosis of long bones, the diaphysis of upper and/or lower limbs, clavicles, or ribs, which was diagnosed by X-ray. The remaining 28 patients were included in the control group (13 females). Patients with hyperostosis of any other localization were excluded.*

Results: *Receiver operating characteristic analysis was performed to determine the minimal injected dose in which there was a risk of developing prostaglandin-induced periostitis. Periostitis was graded as 1 and its absence as 0. Estimated data showed that if the injected dose had increased to 172.5 ng/kg/min, hyperostosis would likely appear in 90% of patients (area under the curve: 0.918; $P < 0.0010$), with sensitivity of 90.0% and specificity of 92.9%. The odds ratio of hyperostosis development was 75.0 ($P < 0.0001$) in the group with a total injected dose ≥ 172.5 ng/kg/min. The relative risk in the same group was 11.6 ($P = 0.0004$).*

Conclusion: *Our study showed that prostaglandin-induced hyperostosis is a dose-related condition. The minimum injected dose of 172.5 ng/kg/min was estimated as a risk of hyperostosis development.*

Keywords

Hyperostosis, Prostaglandin, X-ray, Congenital heart defects, Pediatric surgery.

Core Tip

A retrospective study of infant patients with ductal-dependent congenital heart defects and previous history of preoperative prostaglandin E infusion (> 2 d) who developed hyperostosis of long bones, the diaphysis of upper and/or lower limbs, clavicles, or ribs, was conducted. It is hypothesized that cortical changes are equally related to the dosage and length of infusion of prostaglandins. Nevertheless, our study showed that prostaglandin-induced hyperostosis was mostly a dose-related condition. The risk of hyperostosis development occurred at a minimum injected

dose of 172.5 ng/kg/min.

Introduction

The term hyperostosis is used to describe conditions in which there is an enlargement of the outer portion of a bone. Prostaglandin-induced hyperostosis is caused by prolonged infusion of prostaglandin E (PGE). It commonly involves the diaphysis of long bones of the upper and lower limbs, clavicles, ribs, and scapulae. It must be differentiated from a variety of diseases, such as vitamin deficiencies, Caffey's disease, and multifocal osteomyelitis.

PGE therapy is commonly used to maintain the patency of ductus arteriosus in neonates with ductal-dependent congenital heart defects (CHDs) [1-3]. Reversible cortical hyperostosis of long bones is a known side effect of PGE injections. Since prostaglandin is metabolized rapidly, the infusion must be continuous. The length of infusion correlates with the preoperative period. In some cases, patients may need prolonged courses due to prematurity or infection (including sepsis) or if underweight. Intake of PGE leads to the appearance of side effects including fever, convulsions, rashes, necrotizing enterocolitis, soft tissue swelling, and reversible cortical hyperostosis [4].

Some studies have suggested that periostitis was more dependent on the duration of administration of prostaglandins rather than on the dosage of prostaglandins administered. However, infants with cyanotic CHD, which causes decreased pulmonary blood flow and reduced clearance of PGE, may have a higher systemic concentration of PGE [2,5].

In the Cardiovascular Intensive Care Unit at Republican Scientific and Practical Center of Pediatric Surgery prolonged duration of PGE is commonly used in preoperative patients with complex cyanotic CHD. However, hyperostosis does not develop in every patient with a duration intake of more than 3-4 d.

The aim of this study was to determine the minimum injected dose of PGE at which there is a risk of developing prostaglandin-induced periostitis in infants with ductal-dependent CHDs and to explore the presence of additional factors of cyanotic CHD correlating with hyperostosis development.

Materials and Methods

Inclusion and Exclusion riteria

From 2014 to 2021, 48 infants with ductal-dependent CHD and previous preoperative PGE infusion (> 2 d) who underwent reconstructive cardiac surgery were retrospectively included and separated into two groups. The study group included 20 patients (6 females) who met the inclusion criteria of PGE-induced hyperostosis of long bones, the diaphysis of upper and/or lower limbs, clavicles, or ribs. Hyperostosis was diagnosed by X-ray (Figure 1). Currently, this is the most numerous study group analyzed in the published literature. The 28 remaining patients were included in the control group (13 females). Patients with hyperostosis localized elsewhere were excluded.

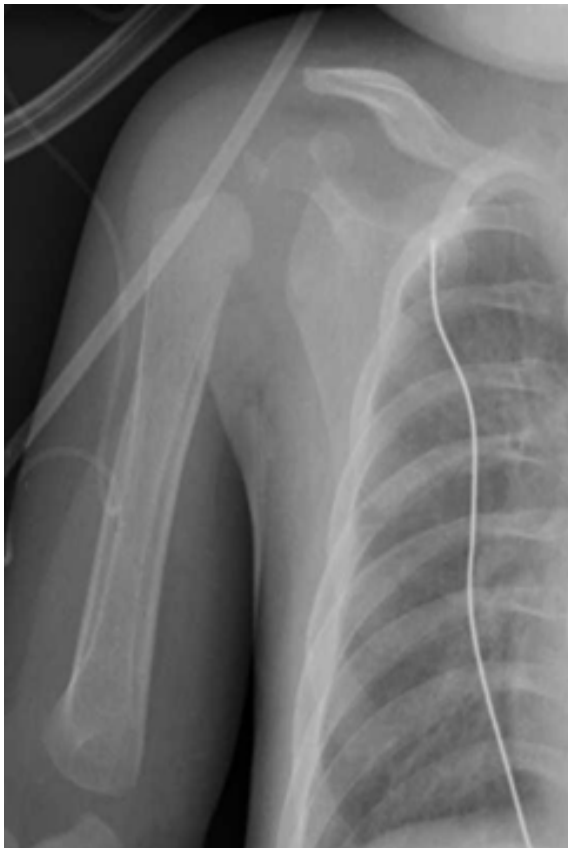

Figure 1: X-ray of an infant with prostaglandin E-induced hyperostosis of long bones, the diaphysis of the upper limbs, and clavicles.

Data Collection

Considering the continuous administration of the drug, the preoperative dose of PGE was determined for each patient in ng/kg/min. In addition, any supplementary laboratory data or instrumental examinations from the patients' medical histories were analyzed.

Statistical Analysis

Statistical analysis was performed in MedCalc® (Copyright © 1993-2023, MedCalc Software Ltd).

Results

Age

The average age at hospitalization in the study group was 8.90 d [95% confidence interval (CI): 0.44-18.24 d]. There was no significant difference in age from the control group (P = 0.6936) (2.25 d; 95%CI: 1.58-2.92 d).

Weight

The average weight of the study group was 2992.2 g (95%CI: 2579.9-3264.4 g). The Shapiro test demonstrated normality of distribution. The average weight of the control group was 3114.2 g (95%CI: 2892.0-3336.3 g). There was no significant difference between the two groups (P = 0.3070) (Figure 2).

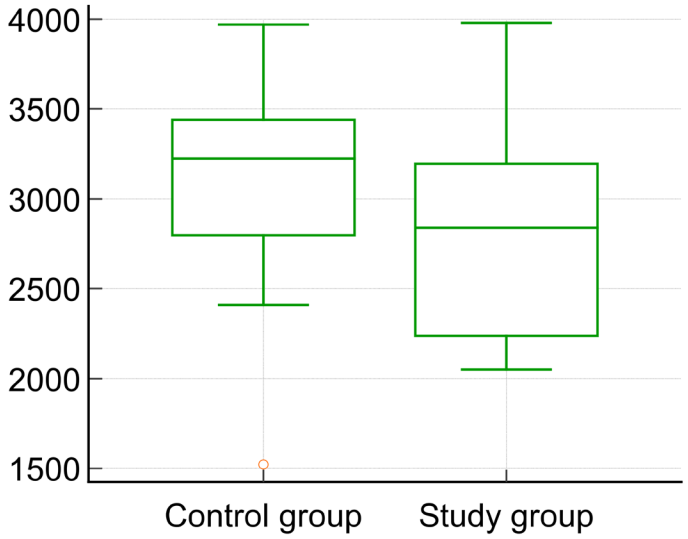

Figure 2: Comparison of body weight (in g) between the study and control groups.

Observed Pathologies

Additional analysis showed the differences in the frequency of the occurrence of pathologies. There was a prevalence in the study group of Tetralogy of Fallot (15% *vs* 3%) and hypoplastic left heart syndrome (35% *vs* 27%) compared to the control group. There was a prevalence in the control group of anomalous pulmonary venous return (10% *vs* 5%), transposition of great arteries (15% *vs* 10%), hypoplastic right ventricle (7% *vs* 5%), and double-outlet ventricle (7% *vs* 0%) (Figure 3).

Size of Ductus Arteriosus

The Mann-Whitney test showed no significant difference in the size of ductus arteriosus (measured by ultrasound on the day of hospitalization) in the two groups (95%CI: 3.4170-6.4152 in the study group *vs* 4.1434-5.1283 in the control group; $P = 0.6002$). There was also no difference when the size of the ductus arteriosus was measured on the day before the operation (95%CI: 3.2678-5.8304 in the study group *vs* 4.0717-5.3208 in the control group; $P = 0.5356$).

Preoperative Procedures and Injected PGE

In addition, a Kruskal-Wallis test was performed to determine the injected PGE dose difference between the group of the patients with and without preoperatively performed procedures. Pulmonary artery banding was marked as 1, Rashkind procedure as 2, and both procedures as 3. If none of these procedures were performed, the patient was marked as 0. The test showed a significant difference between groups 0 and 1 ($P = 0.0006$).

Minimum injected dose of PGE

Receiver operating characteristic analysis was performed to determine the minimum injected dose in which there was a risk of developing prostaglandin-induced periostitis. Periostitis was graded as 1 and its absence as 0, and the amount of injected PGE was used as a criterion. Estimated data showed that if the injected dose increased to 172.5 ng/kg/min, then hyperostosis was predicted to appear in 90% of patients (area under the curve: 0.918; $P < 0.0010$), with a sensitivity of 90.0% and a specificity of 92.9% (Figure 4).

The odds ratio of hyperostosis development in the group with a total injected dose ≥ 172.5 ng/kg/min was 75 ($P < 0.0001$). The relative risk in the same group was 11.6 ($P = 0.0004$).

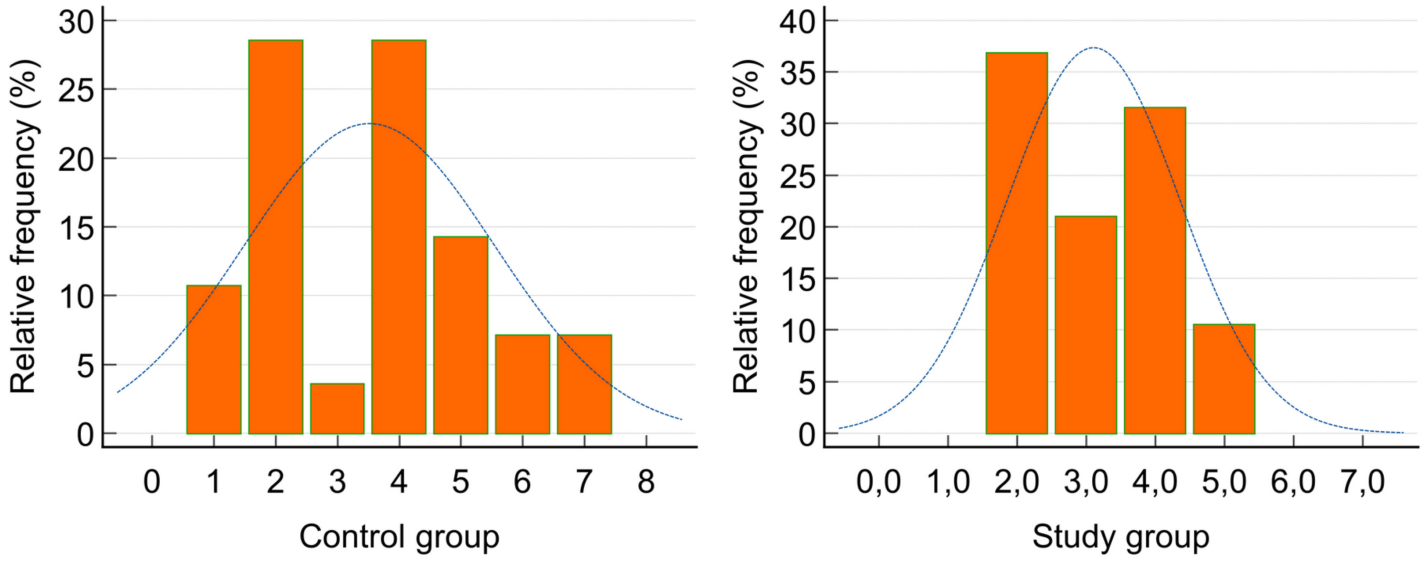

Figure 3: Relative frequency of pathologies in the two groups. A: Study group; B: Control group. 1: Total anomalous pulmonary venous return; 2: Hypoplastic left heart syndrome; 3: Tetralogy of Fallot; 4: Aortic arch anomalies; 5: Transposition of great arteries; 6: Double-outlet ventricle; 7: Pulmonary atresia.

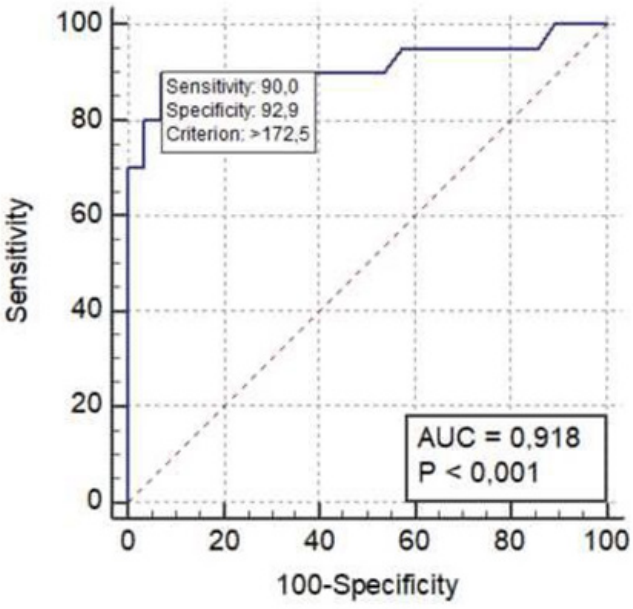

Figure 4: Receiver operating characteristic curve determined the minimum injected dose in which there was a risk of developing prostaglandin-induced periostitis. Periostitis was graded as 1 and its absence as 0. The amount of injected prostaglandin E was used as a criterion. AUC: Area under the curve.

Discussion

Many studies have demonstrated that PGE2 and other prostanoids are abundantly expressed in the bone and can have important roles in skeletal metabolism [6,7]. However, the regulatory function of prostaglandins contributing to the catabolic or anabolic actions of the factor that induces them (and ultimately to bone loss or gain) depends both on the factor inducing prostaglandin production and on the local cellular milieu [7]. After PGE has been discontinued, the process is self-limiting. However, there are a few works concerning its effect on subsequent bone growth and development [8].

After forming the control group, it was shown that in 3 cases the injected dose and duration were quite low, which correlated with an early onset of periostitis. We have not found any previous information about PGE injections given prior to admission at our center. Therefore, these observations may occur due to the high-dose bolus administration after birth at the maternity hospital.

Conclusion

Our study showed that prostaglandin-induced hyperostosis is a dose-related condition. The minimum injected dose of 172.5 ng/kg/min can predict the development of hyperostosis. We have also found features that hyperostosis development could be influenced by ductal-dependent pathology itself, which should be investigated further.

Institutional Review Board Statement

This study was approved by the Ethics Committee of the Republican Scientific and Practical Center of Pediatric Surgery, No. 11 22.03.24.

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