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Effects of phenytoin spray in prevention of fistula formation following cleft palate repair

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ABSTRACT

Background: The effectiveness of topical phenytoin has been reported for the treatment of oral biopsy ulcers, chemotherapy-induced oral mucositis, and chronic periodontitis. This study aimed to investigate the effects of topical phenytoin 2% on the prevention of fistula formation after cleft palate repair.
Method: This randomized clinical trial studied patients with nonsyndromic cleft palate who were referred to a tertiary center and underwent cleft palate repair from March 2010 to February 2015. Patients in the phenytoin group received phenytoin spray 2% for 8 weeks and were compared with an age- and sex-matched control group.
Results: A total of 160 patients in two phenytoin and control groups ($n = 80$ for each group) were recruited to the study. The mean ages of patients in the phenytoin and control groups were 11.42 ± 1.30 and 11.08 ± 1.25 months, respectively. The results showed that six patients (7.5%) in the phenytoin group and 15 patients (18.8%) in the control group formed fistulas during the 6-month follow-up period. There was a significant difference in fistula formation between the phenytoin and control groups ($p = 0.035$). Furthermore, fistula size was significantly smaller in the phenytoin group compared with the control group ($p < 0.001$).
Conclusion: More frequent use of phenytoin spray can be considered, although there is insufficient information on the long-term side-effects of the chosen drug.

1. Introduction

Oral clefting is considered as the most common congenital anomaly of the head and neck and also the second most common congenital anomaly in children after clubfoot. The isolated cleft palate is the rarest presentation of oral clefting (Burg et al., 2016). The prevalence of facial clefts is 0.75–2.14 children per 1000 live births in the Iranian population (Jafari et al., 2017). Based on epidemiological studies, the prevalence of oral cavity cleft palate in the Asian population is higher than that in the European and American populations, with those of black ethnicity showing the lowest risk (Canfield et al., 2014).

Both genetic and environmental risk factors play key roles in cleft palate pathophysiology. Drugs (for example, anticoagulants, anticonvulsants, and bronchodilators), radiation exposure, infections, smoking, and alcohol consumption during pregnancy enhance the risk of cleft palate (Munsie et al., 2011; Kawalec et al., 2015). The effects of drugs are more prominent in the first trimester of pregnancy, especially in the second and third months (Puho et al., 2007). Some studies have reported syndromic cleft palate as concomitant with other malformations, such as congenital septal defect of heart (Stuppia et al., 2011). Van der Woude syndrome represents the most common syndromic type caused by mutations in the GRHL3 and IRF6 genes (Wang et al., 2016; Pegelow et al., 2014).

The goals of cleft palate repair are to produce anatomical closure of the defect and also improvement in palate function. Increased quality of life, with no speech and hearing impairments or regurgitation of oral content into the nasal cavity, is the main outcome of cleft palate repair (Deshpande et al., 2014). According to a recent multicenter analysis by Thiele et al. (2018), approaches to cleft

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palate surgery vary to the extent that it is not possible to compare them; however, postoperative management of cleft-palate complications is generally consistent and effective (Mbuyi-Musanzayi et al., 2018). Fistula formation is a probable complication after cleft palate repair, with an incidence of 21% and recurrence rate of 9% following postoperative fistula repair (Landheer et al., 2010). A study by Hosseinabad et al. (2015) reported a postoperative fistula rate of 23.7%, which was significantly higher in bilateral clefts than in unilateral cases. Moreover, incidence was dependent on cleft extent and surgeon experience (Lu et al., 2010).

Although phenytoin is established as an anti-epileptic medication, the efficacy of topical phenytoin in wound healing has been previously reported (Shaw et al., 2007). It is used for treatment of gastrointestinal tract fistulas, diabetic foot ulcers, and chronic wounds (Sanad et al., 2019; Game et al., 2016). Topical phenytoin has also been shown to be beneficial in the treatment of oral biopsy ulcers (Baharvand et al., 2014a), chemotherapy-induced oral mucositis (Baharvand et al., 2010), and chronic periodontitis (Rashidi Maybodi et al., 2016). Another study has demonstrated the promotion of wound healing in rat hard palate mucosa by topical phenytoin (Hagh et al., 2018).

As a result of this promotion of healing by topical phenytoin, especially in oral ulcers (Baharvand et al., 2014a) and gastrointestinal tract fistulas (Sanad et al., 2019), our study aimed to investigate the effects of topical phenytoin 2% on the prevention of fistula formation after cleft palate repair.

2. Material and methods

This randomized clinical trial studied all patients with a non-syndromic combination of hard and soft cleft palate (ICD-10, Code: Q35.5), who were referred for primary cleft palate repair to a tertiary children's hospital and underwent two-flap palatoplasty (with or without vomerine flap) and intravelar veloplasty from March 2010 to February 2015. The majority of patients had high-arched palate as well as wide cleft palate (Grade II Veau classification). All of the palate repair operations were carried out by an expert cleft palate and lip fellowship surgeon with over 20 years' experience. The inclusion criteria were a complete cleft palate (combined hard and soft palate) and an age of 9–15 months. The exclusion criteria were: revision cleft palate repair, cleft of soft palate, atypical cleft, complications during spray application, a history of seizure, systemic diseases, the taking of anticonvulsant, antihypertension, or immunosuppressant medications, and insufficient medical records.

Children who met the inclusion criteria were stratified (1:1) into the phenytoin and control groups according to their cleft palate width. Allocation to the phenytoin and control groups was performed using a randomized number table. Phenytoin spray was prepared using phenytoin powder (Logman Pharmaceuticals Co., Tehran, Iran) and normal saline. Patients in the phenytoin group received phenytoin spray 2% for 8 weeks and compared with an age- and sex-matched control group. The parents were instructed on how to use the spray by a physician. The phenytoin spray was prescribed every 4 h when the mouth had been washed and dryed after feeding. It was recommended not to feed the child within 1 h of phenytoin spray application.

Demographic information and clinical features of the cleft palate were recorded at baseline and the cleft width was measured prior to operation by the same surgeon. Patients were visited by the surgeon every 2 weeks after palatoplasty and examined for complications associated with cleft palate repair surgery. The interval between surgery and fistula formation was recorded. Fistula features, including size, site, and cause were assessed. In patients without visual signs of fistula formation, a history of nasal regurgitation was also recorded.

The study protocol was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences (registration code: IR.TBZMED.REC.1397.961) and performed in accordance with the Helsinki humanity research declaration (2008). Informed consent was obtained from parents or guardians before enrolling their child to the study. The study was also registered at the Iranian Registry of Clinical Trials (IRCT; registration code: IRCT20180802040678N3).

Statistical Package for Social Science (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The qualitative and quantitative variables with normal distribution were reported as number (%) or mean ± standard deviation (SD). Non-normally distributed variables were expressed as median (min–max). A Kolmogorov–Smirnov test and histogram were used for examination of data distribution. Qualitative variables were analyzed using a Chi-square test. Data with normal and non-normal distributions were analyzed using the Student's *t*-test and Mann–Whitney U-test, respectively. $p \leq 0.05$ was considered as statistically significant.

3. Results

160 patients, including 80 patients in the phenytoin group and 80 patients in the control group, were studied. The mean ages of patients in the phenytoin and control groups were 11.42 ± 1.30 and 11.08 ± 1.25 months, respectively. 39 patients (48.8%) in phenytoin group and 37 patients (46.3%) in the control group were male. The groups were age and sex matched ($p = 0.101$ and 0.874, respectively). The mean follow-up times for the phenytoin and control groups were 25.4 ± 28.92 and 29.36 ± 27.66 months, respectively.

The clefts widths for both groups are shown in Table 1. Six patients (7.5%) in the phenytoin group and 15 patients (18.8%) in the control group showed fistula formation during follow-up (Table 1). There was a significant difference in fistula formation between the phenytoin and control groups ($p = 0.035$). The sites of fistula formation in the control group were at the junction of the soft and hard palate (eight cases), anterior palate (five cases), and soft palate (two cases). In the phenytoin group, fistula formed in the anterior palate (four cases) and the junction of the soft and hard palate (two cases). As shown in Table 1, fistula size at the 8-week intervention and 6 months after surgery was statistically significantly smaller in the phenytoin group compared with the control group ($p < 0.001$ for both). Patients who developed fistulas in the control group had tissue tension (nine cases) and poor postoperative oral hygiene and infection (six cases). In the phenytoin group fistulas were attributed to poor oral hygiene (three cases), tension (one case), pneumonia (one case), and bacterial diarrhea (one case).

The median (min–max) preoperative cleft widths in the patients who developed fistulas in the phenytoin and control groups

Table 1
Clinical features of patients in the phenytoin and control groups.

Feature	Group		*p*-value
	Phenytoin	Control	
Fistula formation			
No	74 (92.5%)	65 (81.2%)	0.035[b]
Yes	6 (7.5%)	15 (18.8%)	
Cleft width[a] (mm)	18.0 (15.0–25.0)	18.5 (15.0–24.0)	0.861[c]
Fistula size at 8-week intervention[a] (mm)	3.5 (2.0–5.0)	10.0 (6.0–12.0)	<0.001[c]
Fistula size 6 months after surgery[a] (mm)	1.5 (0.0–2.5)	8.0 (5.0–10.0)	<0.001[c]

[a] Median (min–max).
[b] Chi-square test.
[c] Mann–Whitney U-test.

were 19.5 (18.0–25.0) and 18.0 (16.0–24.0) mm, respectively. Patients with fistula formation in the phenytoin group had significantly greater preoperative cleft widths compared with those with no fistula ($p = 0.046$); however, this difference was not significant in the control group ($p = 0.726$). During follow-up, the fistula had completely healed in one patient in the phenytoin group.

4. Discussion

Complications associated with cleft palate repair are a major postoperative concern. Despite several advances in methods for reducing complications, postoperative care still needs to be improved. Ethnicity, gender, and socioeconomic status can affect oral clefting. Environmental risk factors include maternal smoking (Sabbagh et al., 2015), alcohol consumption (Bell et al., 2014), maternal obesity (Izedonmwen et al., 2015), zinc deficiency (Skuladottir et al., 2014), and folic acid deficiency (Butali et al., 2013). Nevertheless, the main cause of oral clefting is still unclear.

In the phenytoin group in our study, the site of fistula formation in four of the six patients affected was in the anterior palate. It seems that fistula formation is correlated with the reduced exposure to phenytoin of anteriorly positioned fistulas, suggesting the need for more guidance in applying the spray in order to achieve more application to the anterior region. Regarding the short-term outcome of treatment with topical phenytoin, fistula size 6 months after surgery was significantly lower in the phenytoin group compared with the control group. The results of this study therefore suggest that topical phenytoin reduces fistula formation and accelerates the wound-healing process following cleft palate repair surgery.

The main mechanism behind phenytoin's effects on wound healing remains unclear. Phenytoin increases neovascularization by enhancing fibroblast proliferation and tissue granulation (Patil et al., 2013; Shaw et al., 2011). A reduction in the latent phase before maturation and the inhibitory role of phenytoin on glucocorticoid activity are other suggested mechanisms for the acceleration of wound healing (Shaw et al., 2007). Moreover, phenytoin decreases collagen degeneration by inhibiting phagocytosis (McCulloch and Knowles, 1993). Decreases in bacterial contamination and wound exudate formation are other possible mechanisms (Hasamnis et al., 2010).

The wound healing process takes place in three overlapping phases: inflammatory (1–2 days after wounding), proliferative (4–5 days after wounding), and remodeling (about 3 weeks after wounding and lasting up to 12 months) (Gurtner et al., 2008; Bowden et al., 2016). Re-epithelialization begins within the first few hours following injury, with the healing process initiated over the following 5 days. Recent studies have shown that the oral mucosa healing process is completed 8 weeks after palatoplasty (Sun et al., 2019; Von Den Hoff et al., 2006). According to a recent systematic review, a follow-up period of at least 6 months is required to evaluate fistula formation (Zhang et al., 2017). Accordingly, our study protocol was consistent with recent studies. Due to the increased risk of choking and aspiration associated with using powder and solution forms of phenytoin, we prescribed it in spray form. An increased dose of phenytoin may have systemic effects, so we used a safe dose, as identified by previous studies (Baharvand et al., 2015; Liu et al., 2016).

The effectiveness of topical phenytoin on the healing process in various types of wound has been reported in previous studies (Firmino et al., 2014). To the best of our knowledge, the effects of phenytoin on complications after oral surgery have not yet been studied, although its efficacy with oral biopsy lesions (Baharvand et al., 2014a), oral mucositis (Baharvand et al., 2010), and periodontitis (Rashidi Maybodi et al., 2016) is well understood. In line with other studies on the efficacy of phenytoin on oral lesions, we found a lower incidence of fistula formation after cleft palate surgery. The phenytoin administered in this study differed from that in previous studies on oral lesions in two ways: firstly, it was in spray form, whereas in previous studies mouthwash and oral paste forms of phenytoin were used; secondly, in previous studies phenytoin 0.5–1% was administered, whereas we used phenytoin 2%, which was similar to the dosage used by Sanad et al. in a recent study on anal fistulotomy (Sanad et al., 2019).

Blockage of sodium channels is another proposed mechanism of action of phenytoin, which led to pain relief in patients with oral biopsy ulcers (Baharvand et al., 2014b). Reduction of inflammation by phenytoin has been suggested as another mechanism in improving the healing process and lowering the incidence of complications in patients (Rashidi Maybodi et al., 2016). This anti-inflammatory effect may be one of the leading causes of lower incidence of fistula formation in patients treated with phenytoin spray.

Further studies are required to evaluate the effects of topical phenytoin on complications following cleft palate repair. Due to the limited evidence available on the systemic effects of topical phenytoin, the dosage should be adjusted carefully when phenytoin is prescribed for topical application.

Our study had some limitations. For example, the effects of phenytoin on other cleft-palate complications, such as speech or language problems, were not assessed. Although no patients showed any phenytoin-induced complications, some recent studies have reported phenytoin-induced gingival enlargement. Long-term follow-up periods are needed to evaluate phenytoin-induced systemic and topical complications.

5. Conclusion

Based on the results of this study, more frequent use of phenytoin spray can be considered, although there is insufficient information on the long-term side-effects of this drug. The long-term prescription of topical phenytoin requires more studies to confirm its safety.

References

Baharvand M, Sarrafi M, Alavi K, Jalali Moghaddam E: Efficacy of topical phenytoin on chemotherapy-induced oral mucositis: a pilot study. Daru 18(1): 46–50, 2010

Baharvand M, Mortazavi A, Mortazavi H, Yaseri M: Re-evaluation of the first phenytoin paste healing effects on oral biopsy ulcers. Ann Med Health Sci Res 4(6): 858–862, 2014

Baharvand M, Lafzi A, Ahmad R, Taheri J-B, Mortazavi H, Alirezaei S: Formulation of a new phenytoin-containing mucoadhesive and evaluation of its healing effects on oral biopsy ulcers. Open J Stomatology 4(01): 5, 2014

Baharvand M, Hamian M, Moosavizadeh MA, Mortazavi A, Ameri A: Phenytoin mouthwash to treat cancer therapy-induced oral mucositis: a pilot study. Indian J Cancer 52(1): 81–85, 2015

Bell JC, Raynes-Greenow C, Turner RM, Bower C, Nassar N, O'Leary CM: Maternal alcohol consumption during pregnancy and the risk of orofacial clefts in infants: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 28(4): 322–332, 2014

Bowden LG, Byrne HM, Maini PK, Moulton DE: A morphoelastic model for dermal wound closure. Biomech Model Mechanobiol 15(3): 663–681, 2016

Burg ML, Chai Y, Yao CA, Magee 3rd W, Figueiredo JC: Epidemiology, etiology, and treatment of isolated cleft palate. Front Physiol 7: 67, 2016

Butali A, Little J, Chevrier C, Cordier S, Steegers-Theunissen R, Jugessur A, et al: Folic acid supplementation use and the MTHFR C677T polymorphism in orofacial clefts etiology: an individual participant data pooled-analysis. Birth Defects Res Part A Clin Mol Teratol 97(8): 509–514, 2013

Canfield MA, Mai CT, Wang Y, O'Halloran A, Marengo LK, Olney RS, et al: The association between race/ethnicity and major birth defects in the United States, 1999–2007. Am J Public Health 104(9): e14–e23, 2014

Deshpande GS, Campbell A, Jagtap R, Restrepo C, Dobie H, Keenan HT, et al: Early complications after cleft palate repair: a multivariate statistical analysis of 709 patients. J Craniofac Surg 25(5): 1614–1618, 2014

Firmino F, de Almeida AM, e Silva Rde J, Alves Gda S, Grandeiro Dda S, Penna LH: [Scientific production on the applicability of phenytoin in wound healing]. Rev Esc Enferm USP 48(1): 166–173, 2014
Game FL, Apelqvist J, Attinger C, Hartemann A, Hinchliffe RJ, Londahl M, et al: Effectiveness of interventions to enhance healing of chronic ulcers of the foot in diabetes: a systematic review. Diabetes Metab Res Rev 32(Suppl 1): 154–168, 2016
Gurtner GC, Werner S, Barrandon Y, Longaker MT: Wound repair and regeneration. Nature 453(7193): 314–321, 2008
Hagh LG, Karimi B, Moghimipour E, Abdi Z, Abdolalian F, Rohani A: Histological evaluation of wound healing effect of topical phenytoin on rat hard palate mucosa. J Res Med Dental Sci 6(2): 466–472, 2018
Hasamnis A, Mohanty B, Muralikrishna, Patil S: Evaluation of wound healing effect of topical phenytoin on excisional wound in albino rats. J Young Pharm 2(1): 59–62, 2010
Hosseinabad HH, Derakhshandeh F, Mostaajeran F, Abdali H, Davari HA, Hassanzadeh A, et al: Incidence of velopharyngeal insufficiency and oronasal fistulae after cleft palate repair: a retrospective study of children referred to Isfahan Cleft Care Team between 2005 and 2009. Int J Pediatr Otorhinolaryngol 79(10): 1722–1726, 2015
Izedonmwen OM, Cunningham C, Macfarlane TV: What is the risk of having offspring with cleft lip/palate in pre-maternal obese/overweight women when compared to pre-maternal normal weight women? A systematic review and meta-analysis. J Oral Maxillofac Res 6(1): e1, 2015
Jafari A, Zarea K, Mehregan N: The prevalence of cleft lip and cleft palate and related risk factors among Iranian children from 2000 to 2016: a literature review. Int J Pediatrics 5(4): 4687–4697, 2017
Kawalec A, Nelke K, Pawlas K, Gerber H: Risk factors involved in orofacial cleft predisposition — review. Open Med (Wars) 10(1): 163–175, 2015
Landheer JA, Breugem CC, van der Molen AB: Fistula incidence and predictors of fistula occurrence after cleft palate repair: two-stage closure versus one-stage closure. Cleft Palate Craniofac J 47(6): 623–630, 2010
Liu YS, Li TS, Sun CK, Wei KC, Liu CJ: The application of phenytoin in the treatment of diabetic ulcers. Int Wound J 13(5): 1077–1078, 2016
Lu Y, Shi B, Zheng Q, Hu Q, Wang Z: Incidence of palatal fistula after palatoplasty with levator veli palatini retropositioning according to Sommerlad. Br J Oral Maxillofac Surg 48(8): 637–640, 2010
Mbuyi-Musanzayi S, Kayembe TJ, Kashal MK, Lukusa PT, Kalenga PM, Tshilombo FK, et al: Non-syndromic cleft lip and/or cleft palate: epidemiology and risk factors in Lubumbashi (DR Congo), a case-control study. J Craniomaxillofac Surg 46(7): 1051–1058, 2018
McCulloch CA, Knowles GC: Deficiencies in collagen phagocytosis by human fibroblasts in vitro: a mechanism for fibrosis? J Cell Physiol 155(3): 461–471, 1993
Munsie JW, Lin S, Browne ML, Campbell KA, Caton AR, Bell EM, et al: Maternal bronchodilator use and the risk of orofacial clefts. Hum Reprod 26(11): 3147–3154, 2011
Patil V, Patil R, Kariholu PL, Patil LS, Shahapur P: Topical phenytoin application in grade i and ii diabetic foot ulcers: a prospective study. J Clin Diagn Res 7(10): 2238–2240, 2013
Pegelow M, Koillinen H, Magnusson M, Fransson I, Unneberg P, Kere J, et al: Association and mutation analyses of the IRF6 gene in families with non-syndromic and syndromic cleft lip and/or cleft palate. Cleft Palate Craniofac J 51(1): 49–55, 2014
Puho EH, Szunyogh M, Metneki J, Czeizel AE: Drug treatment during pregnancy and isolated orofacial clefts in Hungary. Cleft Palate Craniofac J 44(2): 194–202, 2007
Rashidi Maybodi F, Haerian-Ardakani A, Nabi-Maybodi M, Nasrabadi N: Effect of 1% phenytoin muco-adhesive paste on improvement of periodontal status in patients with chronic periodontitis: a randomized blinded controlled clinical study. J Dent (Shiraz) 17(3 Suppl): 256–261, 2016
Sabbagh HJ, Hassan MH, Innes NP, Elkodary HM, Little J, Mossey PA: Passive smoking in the etiology of non-syndromic orofacial clefts: a systematic review and meta-analysis. PLoS One 10(3): e0116963, 2015
Sanad A, Emile S, Thabet W, Ellaithy R: A randomized controlled trial on the effect of topical phenytoin 2% on wound healing after anal fistulotomy. Colorectal Dis 21(6): 697–704, 2019
Shaw J, Hughes CM, Lagan KM, Bell PM: The clinical effect of topical phenytoin on wound healing: a systematic review. Br J Dermatol 157(5): 997–1004, 2007
Shaw J, Hughes CM, Lagan KM, Stevenson MR, Irwin CR, Bell PM: The effect of topical phenytoin on healing in diabetic foot ulcers: a randomized controlled trial. Diabet Med 28(10): 1154–1157, 2011
Skuladottir H, Wilcox A, McConnaughey R, Vindenes H, Lie RT: First-trimester nonsystemic corticosteroid use and the risk of oral clefts in Norway. Ann Epidemiol 24(9): 635–640, 2014
Stuppia L, Capogreco M, Marzo G, La Rovere D, Antonucci I, Gatta V, et al: Genetics of syndromic and nonsyndromic cleft lip and palate. J Craniofac Surg 22(5): 1722–1726, 2011
Sun XC, Zhang ZB, Wang H, Li JH, Ma X, Xia HF: Comparison of three surgical models of bone tissue defects in cleft palate in rabbits. Int J Pediatr Otorhinolaryngol 124: 164–172, 2019
Thiele OC, Kreppel M, Dunsche A, Eckardt AM, Ehrenfeld M, Fleiner B, et al: Current concepts in cleft care: a multicenter analysis. J Craniomaxillofac Surg 46(4): 705–708, 2018
Von Den Hoff JW, Maltha JC, Kuijpers-Jagtman AM: Palatal wound healing: the effects of scarring on growth. In: Berkowitz S (ed.), Cleft lip and palate. Berlin, Heidelberg: Springer Berlin Heidelberg, 301–313, 2006
Wang Y, Sun Y, Huang Y, Pan Y, Jia Z, Ma L, et al: Association study between Van der Woude syndrome causative gene GRHL3 and nonsyndromic cleft lip with or without cleft palate in a Chinese cohort. Gene 588(1): 69–73, 2016
Zhang Z, Stein M, Mercer N, Malic C: Post-operative outcomes after cleft palate repair in syndromic and non-syndromic children: a systematic review protocol. Syst Rev 6(1): 52, 2017