Evaluation of pulp vitality using a pulse oximeter in patients undergoing radiotherapy for rhabdomyosarcoma or rhinopharynxcarcinoma

Avaliação da vitalidade pulpar utilizando o oximetro de pulso em pacientes submetidos à radioterapia para rabdomiossarcoma ou carcinoma de rinofaringe

Evaluación de la vitalidad pulpar usando el oxímetro de pulso en pacientes que pasaron por radioterapia para rabdomiosarcoma o carcinoma de rinofaringe

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Resumo

A cavidade oral é altamente suscetível a alterações patológicas devido aos efeitos deletérios da radiação (RI) nos tecidos expostos durante a radioterapia (RT). O objetivo deste estudo foi avaliar a viabilidade do uso do oxímetro de pulso (PO) como instrumento de diagnóstico na avaliação do nível de oxigenação pulpar (% SpO2) de dentes imaturos previamente expostos à RI. A saturação da oxigenação pulpar foi avaliada em quinze crianças ou adolescentes (Grupo RT) que receberam RI prévia há 6,01 anos (SD 4,08 anos), e em quinze pacientes sem história de neoplasias ou quimioterapia ou radioterapia prévia (grupo CO). Como resultado, a %SpO2 média medida no Grupo RT e Grupo CO foi de 86,06% (SD 1,61%) e 91,11% (SD 0,87%), respectivamente. Conclusão: A utilização do oxímetro de pulso adaptado para odontologia na avaliação da vitalidade pulpar em pacientes que receberam radioterapia é viável apresentando nível de SpO2 inferior ao do grupo controle (p<0.05).

Palavras-chave: Polpa dentária; Oximetria; Radioterapia; Rabdomiossarcoma; Carcinoma rinofaríngeo.

Abstract

The oral cavity is highly susceptible to pathological changes due to the deleterious effects of radiation (RI) on tissues exposed during radiotherapy (RT). The aim of this study was to evaluate the feasibility of using pulse oximeter (PO) as a diagnostic instrument for assessing the pulp oxygenation level (%SpO₂) of immature teeth previously exposure to

IR. Pulp oxygenation saturation was evaluated in fifteen children or adolescent patients (Group RT) that received previous IR, 6.01 years ago (SD 4.08 years), and fifteen patients without a history of neoplasms or previous chemotherapy or radiotherapy (CO group). As result, the mean %SpO₂ measured in Group RT and Group CO was 86.06% (SD 1.61%) and 91.11% (SD 0.87%), respectively. Conclusions: The use of the pulse oximeter adapted for dentistry for pulpal vitality evaluation in patients who received radiotherapy is feasible showing lower level of SpO₂ than that of the control group (p<0.05).

Keywords: Dental pulp; Oximetry; Radiotherapy; Rhabdomyosarcoma; Rinopharyngeal carcinoma.

Resumen

Los tejidos de la cavidad oral son altamente suceptibles a las alteraciones patológicas devido a los efectos colaterales de la radiación (RI) originados por la radioterapia (RT). El objetivo de este estúdio fue analizar la viabilidad del uso del oxímetro de pulso (PO) como herramienta para evaluar el nivel de oxígeno pulpar (% SpO2) en dientes inmaduros anteriormente expuestos a RI. La saturación del oxígeno pulpar fue evaluada en quince niños o adolecentes (Grupo RT) que recibieron RT anteriormente hace 6,01 años (SD 4,08 años) y quince pacientes sin historia de neoplasmas o quimioterapia o radioterapia anterior (Grupo CO). Como resultado, la % SpO2 media obtenida en el grupo RT y en el grupo CO fue de 86,06% (SD 1,61%) y 91,11% (SD 0,87%), respectivamente. Conclusiones: La utilización del oxímetro de pulso adaptado para la odontologia en la avaliación de la vitalidad pulpar em pacientes que recibieron radioterapia es viable mostrando um nivel de SpO2 inferior al del grupo control (p<0.05).

Palabras clave: Pulpa dental; Oximetria; Radioterapia; Rabdomiosarcoma; Carcinoma rinofaríngeo.

1. Introduction

Advances in knowledge and technologies used in head and neck radiotherapy (RT) procedures have greatly improved survival rates. To enhance quality of life, it is also essential to maintain good oral conditions before and after ionizing radiation (IR), because patients who receive radiotherapy are highly susceptible to pathological changes in the oral cavity due to the deleterious effects of radiation on the exposed tissues (Sennhenn-Kirchner et al. 2009).

Previous studies have shown that when an erupted tooth is in the radiation pathway, the IR may decrease vascularization, resulting in increased fibrosis and atrophy of the dental pulp (Cooper et al. 1995; Grötz et al. 1998). The same effects were found in immature teeth during the odontogenesis period (Afanasyev & Liubarets 2020), resulting in the interruption of root formation or malformation (Guggenheimer et al. 1975), subsequent early tooth loss, and possibly, changes in facial development (Afanasyev & Liubarets 2020).

To plan an ideal treatment, the pulp status must be determined as part of the endodontic diagnosis. Commonly, the cold test (TPT) is used for this purpose because of its reliability, ease, and availability (Pigg et al. 2016). This diagnostic method assesses the tooth by its neuronal response (Abd-Elmeguid & Yu 2009). Despite its extensive use, thermal stimulation tests are unable to determine pulpal vitality because vitality is dependent on blood supply and oxygenation (Abd-Elmeguid & Yu 2009). In immature teeth, the subjectivity of the response is problematic, as the test results are dependent on the child's understanding and collaboration. Hence, these results are susceptible to misinterpretation (Gopikrishna et al. 2007).

Pulse oximetry (PO) is a noninvasive method commonly used in medicine to determine blood oxygen saturation (SpO₂). Studies have shown that blood microcirculation within the pulp can be measured via the oxyhemoglobin saturation - HgO₂ (Miller et al. 1992; McMorrow & Mythen 2006; Caldeira et al. 2016), and this has recently been achieved in teeth as well (Gopikrishna et al. 2007, Calil et al. 2008; Jafarzadeh & Rosenberg 2009; Pozzobon et al. 2011). The assessment of pulp vitality using pulse oximetry has produced median oxygen saturation levels ranging from 75% (Gopikrishna et al. 2007) to 94% (Schnettler & Wallace 1991).

Pulp tissues exposed to IR in the head and neck region showed microcirculatory changes with a consequent decrease in pulp oxygenation rates (Kataoka et al. 2011, 2016), resulting in temporary loss of dental sensitivity (Garg et al 2015). The altered sensitivity and oxygen saturation tend to return to normal levels after a few weeks (Gupta et al. 2018).

PO adapted for dentistry is a prominent diagnostic method because of its degree of reliability and ease of use (Kataoka et al. 2016; Shahi et al. 2015) and high specificity (Gopikrishna et al. 2007).

There is little information regarding the late effects of IR on the pulp in children and adolescents with a history of head and neck RT. Therefore, this study aimed to evaluate the feasibility of using PO as a diagnostic instrument for assessing the pulp oxygenation level (%SpO₂) of immature teeth previously exposure to IR.

2. Materials and Methods

This study was approved by the Ethics and Research Committee of the Federal University of São Paulo CAA 64688717.9.0000.5505 and authorized by the scientific committee of the Pediatric Oncology Institute GRAACC UNIFESP Ref.: 35/2016. Periapical radiographs of the anterior teeth were used to define the inclusion criteria: upper or lower central incisors, lateral incisors or canines with intact crowns or small restorations (<2mm), teeth without periapical disease, absence of resorptive or degenerative processes, and teeth without endodontic treatment. The criteria for general health were children and adolescents with good clinical health, showing stable SaO₂ rates, when compared to the index finger saturation. Metodology used was similar to used in previous studies (Kataoka et al. 2011, 2016).

Group RT consisted of fifteen patients (a mix of men and women) between the ages of 6 and 30 years who received IR for rhabdomyosarcoma, parameningeal sarcoma or rhinopharynx carcinoma in the head and neck region. In relation to tumor diagnosis, 40% (6 individuals) presented with rhabdomyosarcoma and 60% (9 individuals) presented with carcinoma. The mean radiation dosage received by the patients was 6903.73cGy (SD 2815.38 cGy)

Group CO included 15 patients (a mix of men and women) with the same age range (6-30years) as Group RT, and without a history of neoplasms, chronic diseases, or previous chemotherapy or radiotherapy.

The total number of teeth included for evaluation was 158 in the radiotherapy group (RT) and 336 in the control (CO) group (Table 1).

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	11	12	13	21	22	23	31	32	33	41	42	43	Total	
RT	14	13	14	14	15	14	13	12	11	14	12	12	158	
СО	28	28	30	28	28	29	30	25	29	27	25	29	336	

Table 1. The total number of teeth included for evaluation was in RT and CO groups.

Source: Authors.

The patients were evaluated for pulpal sensitivity and vitality. To exclude non-vital teeth, the pulpal sensitivity was assessed using the cold test (TPT), which involved cooling the dental surface. Difluorodichloromethane Endo-Frost, (Roeko GmbH, Langenau, Germany) was applied to the mid-vestibular tooth surface via a cotton pellet. Index finger saturation and pulp vitality evaluation of the selected tooth was verified using a pulse oximeter Rossmax SA210[®] (Rossmax Swiss GmbH, Heerbrugg, Switzerland) The pulse oximeter was adapted for dental use via the "Y" modified sensor (Figure 1), and these were manually positioned parallel to each other on the vestibular (emitting diode) and palatal/lingual (receiver diode) surfaces, under relative isolation (Figure 2).





Source: Authors.

Figure 2. "Y" sensor positioned on the vestibular and palatal surfaces of the maxillary central incisor.



Source: Authors.

Data were recorded. The Kolmogorov-Smirnov adherence analysis test and the student's t-test were used for statistical analyses.

3. Results

The mean age of Group RT (n=15, 60% male and 40 % female) was 11.47 years (SD 3,42 years). The mean age of patients in Group CO who had never had RT (n=30, 56.67% female and 43.33% male) was 18.83 years (SD 2.56 years). In Group RT, the time elapsed since the last RT exposure was 6.01 years (SD 4.08 years).

All evaluated teeth responded positively to the pulp sensitivity assessment via the cold test using difluorodichloromethane (EndoFrost) allowing their inclusion in the study. The mean %SpO₂ in Group RT and Group CO was 86.06% (SD1.61%) and 91.11% (SD 0.87%), respectively (Table 2).

Table 2. The $\%$ SpO ₂ for each tooth and the mean value of Group RT and Group CO.													
	11	12	13	21	22	23	31	32	33	41	42	43	Mean
RT	83.80	85.00	85.00	87.40	85.36	85.80	88.33	84.63	86.57	89.20	85.00	86,63	86.06±1.61
СО	90.69	90.58	92.60	91.85	91.92	89.80	90.21	90.85	91.40	91.85	90.08	91.47	91.11±0,87

Source: Authors.

The Kolmogorov-Smirnov adherence analysis test demonstrated a normal distribution pattern in both groups. Hence, the student's t-test (Bioestat 5.3, Belém, Pará, Brazil) was used to determine statistically significant differences between the groups (p < 0.0001).

4. Discussion

Although recent knowledge in molecular biology, technology, and support treatment has significantly increased cancer survival rates in children, the sequelae of anti-neoplastic treatment are numerous and can manifest many years after termination of therapy (Wexler 2016; Prasad et al. 2017).

In cases of rare tumors, such as rhabdomyosarcoma, parameningeal sarcoma, and rhinopharynx carcinoma, radiotherapy is the main treatment method for local disease control (Ribassin-Majed et al. 2017). During treatment, these patients receive high doses of radiation (5000-6500cgs) in the head and neck region, which can decrease local vascularization, including the dental pulp (Epstein et al. 2012).

Faria et al. 2014 demonstrated pulp morphologic preservation immediately after irradiation, however in the course of time, RT could affect the pulpal tissues, causing inflammation, and reduced blood circulation and SpO₂ levels with subsequent hypoxia (Kataoka et al. 2011, 2016, Anusha et al. 2017). A previous study demonstrated that the mean SpO₂ levels decreased in the short-term (<6 months) after RT in adults (Kataoka et al. 2011) but the changes did not persist over time (Kataoka et al. 2016).

One limitation of this study was the small number of individuals (n=15) and teeth (n=158) included in the RT group, justified by the specificity of the tumor type and the age range of the children and adolescent patients.

Difficulties in obtaining reliable responses due to patient's fear and anticipatory anxiety in the face of cold sensitivity pulp tests are common (Calil et al. 2008). This occurs more frequently in pediatric oncological patients because these patients are often subjected to extensive treatment, pain-inducing interventions and emotional disorders (Pöder et al 2010). Thus, in these cases, the use of a pulse oximeter adapted for dental use for pulp vitality evaluation has been encouraged by publications that endorsed their efficiency and feasibility (Calil et al. 2008; Kataoka et al. 2011, 2016).

In this study, evaluated teeth in group RT and group CO that presented positive results to the cold sensitivity test showed a mean SpO₂ rate of 86.06% (SD 1.61%) and 91.11% (SD 0.87%) respectively. These results concurred with previous reports, in which the SpO₂ values exceeded 75% (Gopikrishna et al. 2007)

Irradiation induces hyposalivation and pH reduction which are definitively cariogenic, therefore, teeth often present large amount of substantial incipient caries (Silva et al. 2009). This aggression results in a cronic pulpal inflammation showing an asymptomatic irreversible pulpitis that revealed low values of SpO₂. These findings agree with Setzer et al. 2012 that reported a SpO₂ of 83.1% (SD 2.29%) in cases of irreversible pulpitis and Anusha et al. 2017 that showed values of 81.6 % (SD 0.85%) for inflammaded pulp status.

In this study, teeth in Group RT had lower oxygen saturation rates than those in Group CO group (p < 0.0001). These results are different to those reported by Kataoka et al. 2016. In their study, the authors observed no statistical difference between teeth that underwent RT with a maximum average dose of 61.8GY after 4 to 6 years, compared to teeth that had never been exposed to IR. These differences detected in the RT groups in both studies may be due to the patient's age. Individuals in our study showed a mean age of 11.47 years, whereas the average age for participant in the Kataoka et al. 2016 study was 49.4 years at the time of vitality evaluation.

Few studies have analyzed the changes in the immature tooth pulp following exposure to ionizing radiation for head and neck tumors (Kataoka et al. 2011, 2016; Faria et al. 2014; Garg et al 2015). Group RT was composed by children or adolescents with mean age of 11.47 years (SD 3.42 years), thus an incomplete root development was present in most cases of upper lateral incisors and canines. RT in immature tooth could lead to a chronic inflamed pulpal state similar to findings from Gheorghe et al. 2109 that showed histological and immunohistochemicals changes in vital abutment teeth characterized by an asympatomatic irreversible pulpitis who presented a continuous ageing process that reduces perfusion and SpO₂ levels. However, only a histologic examination of the pulp could correlate the pulpal status with its SpO₂.

In conclusion, PO is a practicable method for diagnosing pulpal conditions prior to conservative or endodontic treatment in patients who received radiotherapy for rare tumors (rhabdomyosarcoma, parameningeal sarcoma, and rhinopharynx carcinoma).

5. Conclusions

The findings of this study suggested that: 1) The use of the pulse oximeter adapted for dentistry for pulpal vitality evaluation in patients who received radiotherapy is feasible, and 2) The mean pulpal SpO_2 for irradiated patients was lower than that of the control group. Although the use of the pulse oximeter shows effectiveness in measuring pulp vitality in patients who received radiotherapy, further studies should be carried out.

References

Abd-Elmeguid, A., & Yu, D. C. (2009). Dental pulp neurophysiology: part 2. Current diagnostic tests to assess pulp vitality. *Journal Canadian Dental Association*, 75, 139-43.

Afanasyev, D. E., & Liubarets, S. F. Odontological effects of ionizing radiation (review). (2020). Problems of Radiation Medicine and Radiobiology, 25,18-55.

Caldeira, C. L., Barletta, F. B., Ilha, M. C., Abrão, C. V., & Gavini, G. (2016). Pulse oximetry: a useful test for evaluating pulp vitality in traumatized teeth. Dental Traumatology, 32, 385-9.

Anusha, B., Madhusudhana, K., Chinni, S. K., & Paramesh, Y. (2017). Assessment of Pulp Oxygen Saturation Levels by Pulse Oximetry for Pulpal Diseases – A Diagnostic Study. *Journal of Clinical and Diagnostic Research*, 11, 36-39.

Calil, E., Caldeira, C. L., Gavini, G., & Lemos, E. M. (2008). Determination of pulp vitality in vivo with pulse oximetry. *International Endodontic Journal*, 41, 741-6.

Cooper, J. S., Fu, K., Marks, J., & Silverman, S. (1995). Late effects of irradiation therapy in the head and neck region. *International Journal of Radiation Oncology, Biology, Physics*, 31, 1141-64.

Epstein, J. B., Thariat, J., Bensadoun, R. J., Barasch, A., Murphy, B. A., Kolnick, L., Popplewell, L., & Maghami, E. (2012). Oral complications of cancer and cancer therapy: from cancer treatment to survivorship. *CA Cancer Journal for Clinicians*, 62, 400-22.

Faria, K. M., Brandão, T. B., Ribeiro, A. C., Vasconcellos, A. F., de Carvalho, I. T., de Arruda, F. F., Castro Junior, G., Gross, V. C., Almeida, O. P., Lopes, M. A., & Santos-Silva, A. R. (2014). Micromorphology of the dental pulp is highly preserved in cancer patients who underwent head and neck radiotherapy. *Journal of Endodontics*, 40, 1553-9.

Garg, H., Grewal, M. S., Rawat, S., Suhag, A., Sood, P. B., Grewal, S., & Ahlawat, P. (2015). Dental Pulp Status of Posterior Teeth in Patients with Oral and Oropharyngeal Cancer Treated with Concurrent Chemoradiotherapy. *Journal of Endodontics*, 41, 1830-3.

Gheorghe, A. G., Mercut, V., Popescu, S. M., Mehedinți, M. C., Țuculina, M. J., Olimid, D., Lazăr, A. D., Diaconu, O. A., & Moraru, A. I. (2019). Histological and immunohistochemical aspectsof the atrophic dental pulp modifications of abutment teeth. *Romanian Journal of Morphology and Embryology*, 60, 889-94.

Gopikrishna, V., Tinagupta, K., & Kandaswamy, D. (2007). Comparison of electrical, thermal, and pulse oximetry methods for assessing pulp vitality in recently traumatized teeth. *Journal of Endodontics*, 33, 531-5.

Grötz, K. A., Duschner, H., Kutzner, J., Thelen, M., & Wagner, W. (1998). Histotomography studies of direct radiogenic dental enamel changes. *Mund Kiefer* und Gesichtschirurgie, 2, 85-90.

Guggenheimer, J., Fischer, W. G., & Pechersky, J. L. (1975). Anticipation of dental anomalies induced by radiation therapy. Radiology, 117, 405-6.

Gupta, N., Grewal, M. S., Gairola, M., Grewal, S., & Ahlawat, P. (2018). Dental Pulp Status of Posterior Teeth in Patients with Oral and Oropharyngeal Cancer Treated with Radiotherapy: 1-year Follow-up. *Journal of Endodontics*, 44, 549-554.

Jafarzadeh, H., & Rosenberg, P. A. (2009). Pulse oximetry: review of a potential aid in endodontic diagnosis. Journal of Endodontics, 35, 329-33.

Kataoka S. H, Setzer F. C, Gondim-Junior E, Fregnani E. R, Moraes C. J, Pessoa O. F, Gavini G, & Caldeira C. L. (2016). Late Effects of Head and Neck Radiotherapy on Pulp Vitality Assessed by Pulse Oximetry. *Journal of Endodontics*, 42, 886-9

Kataoka S. H, Setzer F. C, Gondim-Junior E, Pessoa O. F, Gavini G, & Caldeira, C. L. (2011). Pulp vitality in patients with intraoral and oropharyngeal malignant tumors undergoing radiation therapy assessed by pulse oximetry. *Journal of Endodontics*, 37, 1197-200.

McMorrow, R. C., & Mythen M. G. (2006). Pulse oximetry. Current Opinion Critical Care, 12, 269-71.

Miller, M. F., Luckenbach, J., & Chen, C. (1992). Clinical evaluation of a new saturation/hematocrit monitor. *Journal of Extra-corporeal Technology*, 24, 55-7.

Pigg, M, Nixdorf D. R, Nguye, R. H, & Law, A. S. (2016). Validity of Preoperative Clinical Findings to Identify Dental Pulp Status: A National Dental Practice-Based Research Network Study. *Journal of Endodontics*, 42, 935-42.

Pöder U, Ljungman G, & von Essen L. (2010). Parents' perceptions of their children's cancer-related symptoms during treatment: a prospective, longitudinal study. *Journal of Pain and Symptom Management*, 40, 661-70.

Pozzobon M. H, Vieira R S, Alves A. M. H, Reyes-Carmona J, Teixeira C. S, de Souza B D. M, & Felippe W. T. (2011). Assessment of pulp blood flow in primary and permanent teeth using pulse oximetry. *Dental Traumatology*, 27, 184-8.

Prasad S. P, Chinnaswamy G, Vora T, Prasad M, Bansal D, Kapoor G, Radhakrishnan V, Agarwala S, Laskar S, Arora B, Kaur T, Rath G. K, & Bakhshi S. (2017). Diagnosis and Management of Rhabdomyosarcoma in Children and Adolescents: ICMR Consensus Document. *Indian Journal of Pediatrics*, 84, 393–402.

Ribassin-Majed L, Marguet S, Lee A. W M, Ng W. T, Ma J, Chan A T C, Huang P Y, Zhu G, Chua D. T. T, Chen Y, Mai H. Q, Kwong D. L. W, Cheah S. L, Moon J, Tung Y, Chi K. H, Fountzilas G, Bourhis J, Pignon J. P, & Blanchard P. (2017). What Is the Best Treatment of Locally Advanced Nasopharyngeal Carcinoma? An Individual Patient Data Network Meta-Analysis. *Journal of Clinical Oncology*, 35, 498-505

Schnettler, J. M., & Wallace, J A. (1991). Pulse oximetry as a diagnostic tool of pulpal vitality. Journal of Endodontics, 17, 488-90.

Sennhenn-Kirchner S, Freund F, Grundmann S, Martin A, Borg-von Zepelin M, Christiansen H, Wolff H. A, & Jacobs H. G. (2009). Dental therapy before and after radiotherapy--an evaluation on patients with head and neck malignancies. *Clinical Oral Investigations*, 13,157-64.

Setzer, F. C, Kataoka, S. H, Natrielli, F, Gondim-Junior, E, & Caldeira, C. L. (2012). Clinical diagnosis of pulp inflammation based on pulp oxygenation rates measured by pulse oximetry. *Journal of Endodontics*, 38, 880-3.

Shahi, P, Sood, P B, Sharma, A, Madan, M, Shahi, N, & Gandhi, G. (2015). Comparative Study of Pulp Vitality in Primary and Young Permanent Molars in Human Children with Pulse Oximeter and Electric Pulp Tester. *International Journal of Clinical Pediatric Dentistry*, 8, 94–98.

Silva, A. R. S, Alves, F. A, Antunes, A, Goes M. F, & Lopes, M. A. (2009). Patterns os demineralization and dentin reactions in radiation-related caries. Caries Research, 43, 43-49.

Wexler, L H. (2016). Metastatic Rhabdomyosarcoma: Still Room for Improvement. Journal of Clinical Oncology, 34, 105-6.