European Review for Medical and Pharmacological Sciences 2018; 22: 8497-8501

^{99m}Tc-diphosphonates bone scintigraphy for vitality evaluation in cleft palate

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Abstract. – Cleft of the lip, palate and alveolus are congenital oro-maxillofacial malformation with an established treatment protocol. At present, there is great interest in the alveolar bone grafting procedures that involve the use of platelet-rich-plasma (PRP), to enhance bone formation and specifically to promote bone graft healing in head and neck tissues regeneration. The aim of this retrospective case report study was to assess the condition and viability of the standard bone grafting in association with PRP (platelet rich plasma) to enhance osteogenesis and maintain osteointegration in alveolar cleft with a follow up of eight years from the surgical procedure. The viability of bone grafts was documented by means of head bone scintigraphy (^{99m}Tc-MDP). The scintigrams revealed the decreased uptake at the cleft region and the increased uptake at the adjacent alveolus of the cleft. From these findings we suggest that platelet concentrates decrease the need of further surgical intervention in cleft palate patients. In addition, scintigraphy may be useful to evaluate postoperative bone formation in the alveolar cleft.

Key Words:
Cleft palate, Bone scintigraphy, Platelet-rich plasma (PRP), Bone grafting, ^{99m}Tc-MDP.

Introduction

Clefts of the lip, palate and alveolus are the commonest congenital anomaly to affect the oro-maxillofacial facial region, who occurs in about one in 700 live births worldwide, for which efforts have been made to classify and repair, since the time of Veau (1931)[1,2]. The principal concern in cleft palate repair is closure of the physical defect, with the best velopharyngeal (VP) function and perfect speech, without affecting the maxillofacial growth or hearing[3-5]. Velopharyngeal insufficiency and oronasal fistula represent the most common complication after cleft palate repair[5,6]. Platelet rich plasma (PRP) is an autologous platelet concentrate which contains several growth factors that are useful for enhancing wound healing and bone regeneration in surgical procedures[7,8]. The main uses of PRP to date are in head tissues regeneration, especially in dental and maxillofacial surgery, to repair defects caused by dental extraction, or tumor resection, as well as for alveoloplasty, and has proven successful outcomes when used in combination with bone curettage in the treatment of refractory bisphosphonate-related osteonecrosis of the jaw[9-11]. Other specialties have investigated its effect in surgical procedures such as acromioplasty, arthroscopy, rhytidectomy with fat grafts, skin wounds and infiltration due to ankle ligament injury[9]. Surgical techniques, their variations, and the outcome and rehabilitation procedures for cleft palate are constantly evolving, and are very well described in the available literature[12], since, in the recent years, there is an increasing of studies regarding the use of platelet concentrates and growth factors, such as PRP, in the surgical management of the cleft palate[13,14]. The clinically successful incorporation of a graft depends on a biologic complex process, including sufficient blood supply and vitality of osteoblasts[15,16]. Several methods[17,18] have been described to monitor the vascular status of the graft, as well the clinical evalua-

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tion of graft healing is highly subjective, many diagnostic techniques are used, including bone scintigraphy. Although radiological evaluations can reveal changes in bone density, they cannot provide information regarding osteogenesis and progression[18]. Nuclear medicine procedures allow the study of physiological and pathophysiological pathways and provide functional images. Biological or pathological processes can be studied depending by the radiopharmaceutical administered and current technologies allow to obtain images with high resolution and which greatly increase the accuracy of each diagnostic procedure[19-21]. We describe a patient who has been treated with autologous bone grafting with PRP and, at our knowledge, for the first time in literature, investigated with skeletal scintigraphy with ^{99m}Tc-methylen-diphosphonates (^{99m}Tc-MDP) in order to have information on the long-time outcome of the treatment.

Case Study

This study was carried on a single pediatric patient (9 y.o. of age) suffering from complete cleft palate with a follow up after 8 years from the surgical procedure. This study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from patient parents. Secondary alveolar bone grafting, according to Giudice et al[22] was performed using the standard surgical methodology for secondary alveolar bone grafting, in addition to PRP.

PRP was prepared from whole blood that was drawn into a closed system with the addition of citrate and the sampling kit was processed by an automatic biochemical system. The PRP produced was in liquid form and mixed with a solution at pH10 for being sprayed by a spray-pen during the surgical technique of bone grafting[22]. ^{99m}Tc-MDP bone scintigraphy was performed before the treatment and repeated after 6 months from the bone grafting and then after 8 years (Figure 1 A-C).

All the exams were performed two hours after the intravenous administration of ^{99m}Tc-MDP with different doses according to the age and weigh of the patients[23]. Tomographic (Single Photon Emission Tomography, SPECT) images were acquired with a SPECT/CT camera GE Discovery 670 dual-headed (GE Healthcare, Haifa, Israel) using a specific protocol (energy window 120-140 keV, high-resolution parallel-hole collimators, 128 × 128 matrix size, 360°

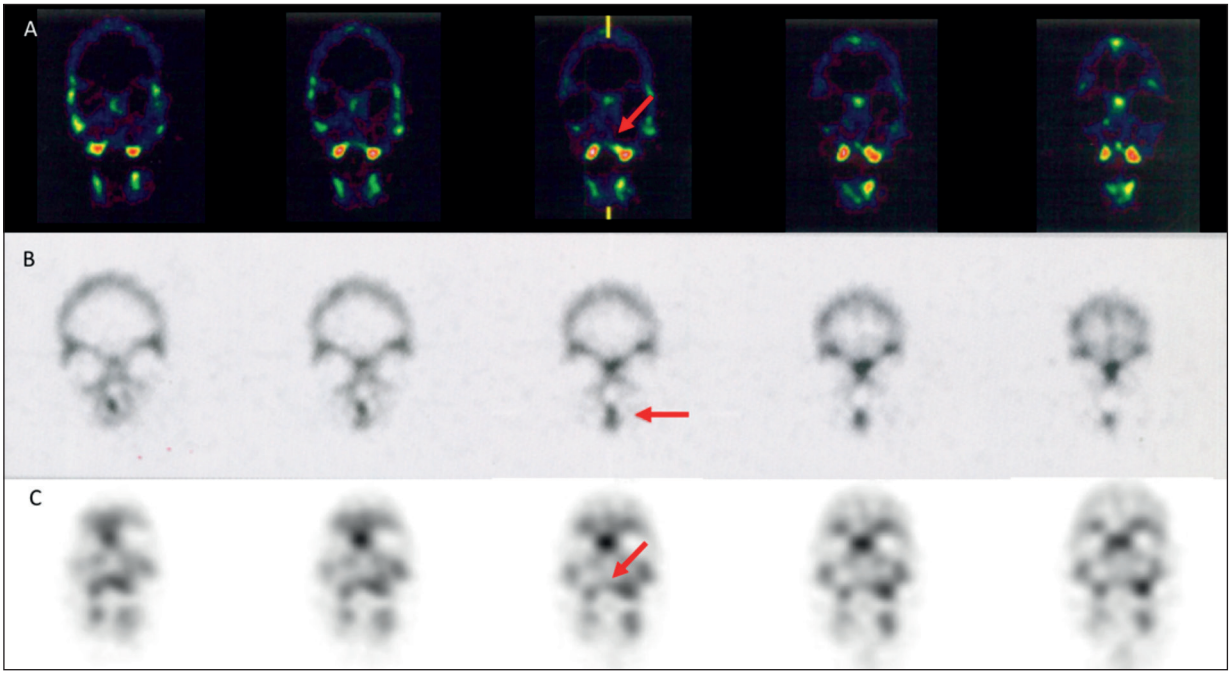

Figure 1. **(A)** Coronal images of the SPECT bone scintigraphy performed before treatment show an area of lack uptake of ^{99m}Tc-MDP along the midline of the maxillary bone (*red arrow*). **(B)** Coronal images of bone scintigraphy performed 6 months after the treatment show intense uptake of ^{99m}Tc-MDP in the same previously missing site (*red arrow*). **(C)** The Coronal images 8 years after the surgical procedure show the homogeneous distribution of ^{99m}Tc-MDP in the maxillary bone.

acquisition, scan mode step and shoot 10 s, view angle 3°, 120 views). The projection images were iteratively reconstructed using a Gaussian filter. Coronal, sagittal and transaxial slices of the mandibular tomograms were thus generated and analyzed. Images before treatment showed the lack of ^{99m}Tc-MDP uptake in the median line of the maxillary bone, in correspondence with the congenital malformation (Figure 1 A). Instead, the images performed 6 months after the treatment showed an intense ^{99m}Tc-MDP uptake in the same site, that is, exactly the site of the bone-grafting procedure (Figure 1 B). The follow-up images showed homogeneous ^{99m}Tc-MDP uptake in all the maxillary bone, demonstrating the perfect integration of the new tissue with the native bone (Figure 1 C).

Discussion

The conventional time for secondary alveolar cleft repair is between 6 and 12 years[22,24]. The success of the reconstruction of the alveolar cleft is determined by the amount of bone formation in the cleft, bone height of the alveolar ridge and the position of the bone in the cleft; besides healing using PRP in our study was similar to other reported worldwide researches[13,22,24,25]. Bone growth problems can be analyzed with ^{99m}Tc-MPD. Bone scintigraphy with radioactive tracers has found widespread use in the imaging of bone blood flow and metabolism. ^{99m}Tc-diphosphonates are highly sensitive for blood flow and metabolic activity of bone tissue[17]. In bone scintigraphy, the uptake of the radiopharmaceutical depends both on an adequate delivery system and on a living network of osteocytes. Bone scintigraphy is an easy, non-invasive and effective modality in the assessment of postoperative graft viability[26]. Single photon emission computed tomography (SPECT) should be favored rather than conventional planar scanning, because of the complex anatomy of the cranio-maxillofacial region. SPECT reconstruction in bone scintigraphy was found to be an excellent tool in diagnosis and follow-up of the cranio-maxillofacial bony structures, as it is widely used to assess bone graft viability in mandibular reconstruction[17,18]. The major advantage of conventional SPECT over planar imaging is the improvement in lesion contrast by enhancing the signal-to-noise ratio by removal of superimposed activity, both anterior and posterior to the area of interest. Therefore, the anatomic description of the process is better, which is particularly important in the mandible with its complicated 3-D structure. ^{99m}Tc-MPD SPECT scanning of the head and neck area, is useful to assess microvascular success or failure and allows a better description of the bone graft without any superimposing effects and with no additional radiation burden to the patient; in addition, the follow-up investigations can assess treatment results far better[17,27-29].

Conclusions

The case described here shows that PRP mixed with autologous bone graft seems to be an effective, safe and low-cost technique for the surgical management of cleft palate. In fact, usage of autologous PRP in complete cleft palate repair is simple and effective. Furthermore, it can decrease the occurrence of oronasal fistula and also significantly improves the grade of nasality and velopharyngeal closure, decreasing the need for further surgical intervention in cleft palate patients. Bone scintigraphy performed within a short and long follow-up after the cleft palate reconstruction is a useful tool to monitor the viability and early complications of vascularized mandibular bone grafts and allow the long-time assessment. SPECT is strongly recommended because contribute to the interpretation of the bone scans and to precise assessment of graft viability. However, there is a need for similar prospective studies to investigate the long-term effectiveness of the proposed procedure.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

G.D. and C.F. gave a scientific contribution for data interpretation; A.C wrote the first draft of the manuscript and supervised diagnostic imaging procedure; A.B. conceived the study and contributed to the study design, data analysis and interpretation, and manuscript revision; S.C. was responsible for bibliographic research, patient management and data collection; N.A.A. coordinate the research; F.I. and G.R. made substantial contributions to the conception and design of the study, diagnosis and coordination, supervised the manuscript and gave final approval of the version to be published. All the authors have read and approved the final manuscript.

References

1) Gupta C, Mehrotra D, Mohammad S, Khanna V, Kumar Singh G, Singh G, Chellappa AA, Passi D. Alveolar bone graft with platelet rich plasma in cleft alveolus. J Oral Biol Craniofac Res 2013; 3: 3-8.
2) Boyne PJ, Sands NR. Secondary bone grafting of residual alveolar and palatal clefts. J Oral Surg 1972; 30: 87-92.
3) Goodacre T, Swan MC. Cleft lip and palate: current management. Paediatr Child Health 2008; 18: 283-292.
4) Stein S, Dunsche A, Gellrich NC, Harle F, Jonas I. One or two stage palate closure in patients with unilateral cleft lip and palate: comparing cephalometric and occlusal outcomes. Cleft Palate Craniofac J 2007; 44: 13-22.
5) El-Anwar MW, Nofal AA, Khalifa M, Quriba AS. Use of autologous platelet-rich plasma in complete cleft palate repair. Laryngoscope 2016; 126: 1524-1528.
6) Jackson IT. Closure of secondary palatal fistulae with intra oral tissue and bone grafting. Br J Plast Surg 1972; 25: 93-105.
7) Dohan Ehrenfest DM, Del Corso M, Inchingolo F, Sammartino G, Charrier JB. Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in human cell cultures: growth factor release and contradictory results. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110: 418-421.
8) Samani MK, Saberi BV, Ali Tabatabaei SM, Moghadam MG. The clinical evaluation of platelet-rich plasma on free gingival graft's donor site wound healing. Eur J Dent 2017; 11: 447-454.
9) Inchingolo F, Cantore S, Dipalma G, Georgakopoulos I, Almasri M, Gheno E, Motta A, Marrelli M, Farronato D, Ballini A, Marzullo A. Platelet rich fibrin in the management of medication-related osteonecrosis of the jaw: a clinical and histopathological evaluation. J Biol Regul Homeost Agents 2017; 31: 811-816.
10) Crincoli V, Ballini A, Di Comite M, Tettamanti L, Coscia MF, Mastrangelo F, De Vito D. Microbiological investigation of medication-related osteonecrosis of the jaw: preliminary results. J Biol Regul Homeost Agents 2015; 29: 977-983.
11) González-Sánchez JG, Jiménez-Barragán K. Closure of recurrent cleft palate fistulas with plasma rich in growth factors. Acta Otorrinolaringol Esp 2011; 62: 448-453.
12) Stein MJ, Zhang Z, Fell M, Mercer N, Malic C. Determining postoperative outcomes after cleft palate repair: a systematic review and meta-analysis. J Plast Reconstr Aesthet Surg 2018; S1748-6815: 30312-30317.
13) Bezerra BT, Pinho JNA, Figueiredo FED, Brandão JRMCB, Ayres LCG, da Silva LCF. Autogenous bone graft versus bovine bone graft in association with platelet-rich plasma for the reconstruction of alveolar clefts: a pilot study. Cleft Palate Craniofac J 2018; 1: 1055665618770194.
14) van Hout WM, Mink van der Molen AB, Breugem CC, Koole R, Van Cann EM. Reconstruction of the alveolar cleft: can growth factor-aided tissue engineering replace autologous bone grafting? A literature review and systematic review of results obtained with bone morphogenetic protein-2. Clin Oral Investig 2011; 15: 297-303.
15) Arden RL, Burgio DL. Bone autografting of the craniofacial skeleton: clinical and biological considerations. Am J Otolaryngol 1992; 13: 328-341.
16) Goldberg VM, Shaffer JW, Field G, Davy DT. Biology of vascularized bone grafts. Orthop Clin North Am 1987; 18: 197-205.
17) Schimming R, Juengling FD, Lauer G, Schmelzeisen R. Evaluation of microvascular bone graft reconstruction of the head and neck with 3-D 99mTc-DPD SPECT scans. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000; 90: 679-685.
18) Buyukdereli G, Guney IB, Ozerdem G, Kesiktas E. Evaluation of vascularized graft reconstruction of the mandible with Tc-99m MDP bone scintigraphy. Ann Nucl Med 2006; 20: 89-93.
19) Altini C, Niccoli Asabella A, Di Palo A, Fanelli M, Ferrari C, Moschetta M, Rubini G. 18F-FDG PET/CT role in staging of gastric carcinomas: comparison with conventional contrast enhancement computed tomography. Medicine (Baltimore) 2015; 94: e864.
20) Rubini G, Altini C, Notaristefano A, Merenda N, Rubini D, Ianora AA, Asabella AN. Role of 18F-FDG PET/CT in diagnosing peritoneal carcinomatosis in the restaging of patient with ovarian cancer as compared to contrast enhanced CT and tumor marker Ca-125. Rev Esp Med Nucl Imagen Mol 2014; 33: 22-27.
21) Niccoli Asabella A, Notaristefano A, Rubini D, Altini C, Ferrari C, Merenda N, Fanelli M, Rubini G. 18F-FDG PET/CT in suspected recurrences of epithelial malignant pleural mesothelioma in asbestos-fibers-exposed patients (comparison to standard diagnostic follow-up). Clin Imaging 2013; 37: 1098-1103.
22) Giudice G, Cutrignelli DA, Leuzzi S, Robusto F, Sportelli P Nacchieri E. Autologous bone grafting with platelet-rich plasma for alveolar cleft repair in patients with cleft and palate. Ann Ital Chir 2016; 87: 5-12.
23) Lassmann M, Treves ST. Pediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (Version 1.5.2008) and the 2010 North America consensus guideline. Eur J Nucl Med Mol Imaging 2014; 41; 1036-1041.
24) Guo J, Li C, Zhang Q, Wu G, Deacon SA, Chen J, Hu H, Zou S, Ye Q. Secondary bone grafting for alveolar cleft in children with cleft lip or cleft lip

and palate. Cochrane Database Syst Rev 2011; 6: CD008050.

25) Dohan Ehrenfest DM, Del Corso M, Inchingolo F, Charrier JB. Selecting a relevant in vitro cell model for testing and comparing the effects of a Choukroun's platelet-rich fibrin (PRF) membrane and a platelet-rich plasma (PRP) gel: tricks and traps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110: 409-411.

26) Aydogan F, Akbay E, Cevik C, Kalender E. Blood-pool SPECT in addition to bone SPECT in the viability assessment in mandibular reconstruction. Eur Rev Med Pharmacol Sci 2014; 18: 587-592.

27) Talo Yildirim T, Güncü GN, Colak M, Nares S, Tözüm TF. Evaluation of maxillary sinus septa: a retrospective clinical study with cone beam computerized tomography (CBCT). Eur Rev Med Pharmacol Sci 2017; 21: 5306-5314.

28) Zhang XL, Wang YM, Chu K, Wang ZH, Liu YH, Jiang LH, Chen X, Zhou ZY, Yin G. The application of PRP combined with TCP in repairing avascular necrosis of the femoral head after femoral neck fracture in rabbit. Eur Rev Med Pharmacol Sci 2018; 22: 903-909.

29) Zhang XL1, Shi KQ, Jia PT, Jiang LH, Liu YH, Chen X, Zhou ZY, Li YX, Wang LS. Effects of platelet-rich plasma on angiogenesis and osteogenesis-associated factors in rabbits with avascular necrosis of the femoral head. Eur Rev Med Pharmacol Sci 2018; 22: 2143-2152.