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To the Editor,

Inherited epidermolysis bullosa (EB) consists of different genetically heterogeneous skin and mucosal disorders due to a number of defects in the synthesis of proteins involved in the adhesion of the epithelium to the connective tissues; the oral cavity is commonly involved but there are very few published data about potential treatment.[1]

Four main EB types are described: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome (KS); these subtypes are currently defined by mode of transmission together with a combination of phenotypic, ultrastructural, immunohistochemical, and molecular findings.[2]

In the last years, we have performed two clinical studies for the management of oral ulcerations in EB patients. Firstly, we tested the efficacy and safety of a platelet gel derived from cord blood (CBPG) with photobiomodulation therapy (PBMT) for the treatment of EB oral lesions, with good pilot results.[3] Following this, a split-mouth randomized trial was conducted showing that the use of CBPG in combination with PBMT was superior to the use of CBPG alone.[4] The only thing left to prove was the usefulness of laser biostimulation in this particular treatment method; bearing this in mind, we have then decided to investigate the differences in the use of the PBMT alone when compared with the use of CBPG in combination with PBMT. The obtained results are here reported.

Briefly, the PBMT can be used to stimulate wound healing, having different intracellular biological reactions to stimulate regenerative abilities, without undesired adverse effects, reducing also the pharmacological support. To date, due to its analgesic, anti-inflammatory, and bio-modulating properties, it is considered a favourable method to treat different kind of lesions on mucosal surfaces.[5] Autologous and allogeneic platelet (PLT) preparations, traditionally obtained from adult blood platelets, are rich in regenerative growth factors, valuable for the treatment of chronic wounds. Recent findings on multiple biological properties of human umbilical cord blood (CB), and its high level of viral safety, prompted one group to produce PLT gel from cord blood, and another to detail the effectiveness of CBPG for the treatment of inherited EB skin lesions.[6,7]

Included in this new split-mouth randomized analysis were patients with inherited EB (Table 1), who presented with multiple oral erosions, having at least two bilateral lesions, also if not in the same anatomical region. Different treatment options were discussed, and all patients submitted written informed consent before enrolment. The Ethics review board of the "Azienda Ospedaliera Città della Salute e della Scienza of Turin", Turin, Italy, approved the study (prot. n° 0089210_CS/585).

CBPG was prepared, transferred into 10 mL storage bags (Biomed Device, Modena, Italy) and cryopreserved at -80°C without the addiction of any cryoprotectant, as previously described.[3,4]

The 10 mL bags were collected in the morning of the scheduled appointment and transported at the CIR-Dental School in less than 1 hour. The FPC was then heated at 37° C using a Plasmaterm H warming oven (BTI Biotechnology Institute North America, USA) and immediately applied on to the oral lesion alone followed by PBMT (GROUP A). The other group of intervention (GROUP B) underwent only PBMT.

A gallium-aluminum-arsenide (Ga-Al-As) diode laser (Raffaello, DMT S.r.l. - Via Nobel, 33 - 20851 Lissone (MB), Italy) was used for the purpose. Patients were exposed to a continued 645-nm red light. A "spot" technique was used, not in contact (2 mm distance), covering all the mucosal lesions and also the peri-lesional tissues up to 0.5 cm and the probe was held perpendicularly. A collimated Gaussian probe, with a spot size of 0.5 cm^2, was used (energy density: 8 J/cm^2; power density: 500 mW/cm^2; total delivered energy: 4 J; power: 250 mW; delivery time per point: 16 seconds).

The choice of which lesion had to be treated with one of the two different approaches was taken by flipping a coin. As previously, the protocol was performed over a 3-day period (one application each day). Pain, size of lesions and eventually adverse effects were collected before and after the proposed protocol and after 7 days from the 3rd session. Complete resolution of the clinical signs (complete response) was defined as the disappearance of all erosive lesions. The symptoms score was obtained using a Visual Analogue Scale (VAS). The stability of the obtained result in the follow up period was also assessed (at 12 and 24 weeks after the end of the therapy).

Thirty-four oral lesions were treated (Table 1); differences in outcome measures are reported in Table 2. No statistical difference was reported comparing the outcome measures stratifying the data for the different intraoral sites, gender, age and type of EB ($P>.05$); a statistically significant difference was observed for reported pain and clinical size from the first day of treatment provided for both groups (Table 2). One week after the end of the proposed protocol, all patients got statistically better. After 6 months, patients treated with application of CBPG followed by PBMT displayed better results for symptoms and lesions' sizes; in particular, when comparing obtained data during the control at day 180 and at day 10, we reported a statistical significant difference only for patients treated with CBPG followed by PBMT (Table 2).

In the follow-up period, no reported complications or therapy side effects were detailed in any of the

treated cases. Patients were all satisfied with the outcome.

As said, very recently we have reported that PBMT is able to improve the use of CPGC within the oral cavity (being the latter less advantageous if used alone), but we never showed the properties of PMBT alone in EB patients.[4]

As previously described, due to its analgesic, anti-inflammatory, and bio-modulating properties, PBMT is considered a favourable method to treat different kind of lesions on mucosal surfaces, having proper regenerative effects.[8] Moreover, PBMT is easy to perform, and does not increase morbidity or presents side effects, especially for younger people.

In our previous report we used laser equipment able to give high doses of energy density, exploiting its suppressive action good in reducing pain. However, due to recent literature data,[9-11] we obtained a new laser machine and we started using a wave length in the red spectrum, utilizing a more superficial action than it is more useful to treat expressly mucosal disorders. In particular, energy density of 8 J/cm^2 has been shown to be more effective in healing process by presence of more collagen deposition, increase activity of myofibroblast, and the presence of clear skin adnexa.[12]

The two modalities of treatment showed both good results in terms of less symptoms reported and decrease of sizes of interest; however, patients treated with application of CBPG followed by PBMT showed greater stability of the obtained results, with a statistically significant data regarding the symptoms still reported after 6 months (P=.021); differently, the laser alone did have good performances in the immediate period after the applications but not still statistically significant in the long term (P=.158).

In conclusion, after 3 years of continuous studies, we finally suggest that PBMT could be use together with CBPG as treatment of choice for patients with oral erosive lesions due to EB. However, considering the difficulty in obtaining the CBPG, even the use of laser photobiomodulation therapy alone can be considered an excellent therapeutic aid, especially for the short term.

REFERENCE

1. Fine JD, Eady RAJ, Bauer JA *et al*. The classification of inherited epidermolysis bullosa (EB): report of the third international consensus meeting on diagnosis and classification of EB. *J Am Acad Dermatol* 2008; **58**: 931-950.

2. Fine JD, Bruckner-Tuderman L, Eady RA *et al*. Inherited epidermolysis bullosa: updated recommendations on diagnosis and classification. *J Am Acad Dermatol* 2014; **70**: 1103-1126.

3. Sindici E, Astesano S, Fazio L *et al*. Treatment of Oral Lesions in Dystrophic Epidermolysis Bullosa: A Case Series of Cord Blood Platelet Gel and Low-level Laser Therapy. *Acta Derm Venereol* 2017; **97**: 383-384.

4. Sindici E, Giuliano B, Astesano S *et al*. Cord blood platelet gel alone or in combination with photobiomodulation therapy for the treatment of oral ulcerations in patients with epidermolysis bullosa: A pilot clinical comparative study. *Photodermatol Photoimmunol Photomed* 2018; **34**: 269-272.

5. Agaiby A, Ghali L, Wilson R, Dyson M. Laser modulation of angiogenic factor production by T-lymphocytes. *Lasers Med Sci* 2000; **26**: 357-363.

6. Parazzi V, Lazzari L, Rebulla P. Platelet gel from cord blood: a novel toll for tissue engineering. *Platelets* 2010; **21**: 549-554.

7. Tadini G, Guez S, Pezzani L *et al*. Preliminary evaluation of cord blood platelet gel for the treatment of skin lesions in children with dystrophic epidermolysis bullosa. *Blood Transfus* 2015; **13**: 153-158.

8. Spanemberg JC, Figueiredo MA, Cherubini K, Salum FG. Low-level Laser Therapy: A Review of Its Applications in the Management of Oral Mucosal Disorders. *Altern Ther Health Med* 2016; **22**: 24-31.

9. Calisto FC, Calisto SL, Souza AP *et al*. Use of low-power laser to assist the healing of traumatic wounds in rats. *Acta Cir Bras* 2015; **30**: 204-208.

10. Wagner VP, Meurer L, Martins MA *et al*. Influence of different energy densities of laser phototherapyon oral wound healing. *Journal of biomedical optics* 2013; **18**: 128002.

11. Antunes HS, Schluckebier LF, Herchenhorn D *et al*. Cost-effectiveness of low-level laser therapy (LLLT) in head and neck cancer patients receiving concurrent chemoradiation. *Oral Oncol* 2016; **52**: 85-90.

12. Diwan MF, Abid TA. The effect of different doses of 660 nm laser therapy on open skin wound healing in Wistar rats. *Kufa Journal for Veterinary Medical Sciences* 2016; **7**: 130-137.