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Editorial

Current management of complicated infantile hemangiomas: Atenolol or Propranolol?

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Manejo actual de los hemangiomas infantiles complicados: ¿Atenolol o Propranolol?

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Infantile hemangiomas are the most common vascular tumor in childhood, occurring in more than 10% of infants in their first year of life [1, 2]. The vast majority appear weeks after birth as telangiectatic patches, which grow rapidly and diffusely until before the age of 6 months, until they become reddish, delimited, dome-shaped protuberances in deep areas [3]. They are mainly located on the face and neck. From the age of one year, these lesions grow parallel to the child's development. The regression of the lesions is almost 100% at 10 years of life [1]. However, depending on the evolution and expansion of the lesions, they can become complicated and bleed uncontrollably, ulcerate and cause pain, disfigure the face, hinder activities of daily living, compromise the child's functional ability and substantially influence mental health [2]. This is not to mention that hemangiomas are associated with certain syndromes such as the PHACES (Posterior fossa malformations/Hemangiomas/Arterial anomalies/Cardiac defects/Eye abnormalities/Sternal cleft/Supraumbilical raphe syndrome) or PELVIS/SACRAL/LUMBAR (Perineal hemangioma/External genitalia malformations/Lipomyelomeningocele/Vesicorenal abnormalities/Imperforate anus/Skin tag), which hinder the management and make the recovery process less tolerable [1-4].

For these complicated hemangiomas, the use of beta-blockers has been described as effective, but not entirely safe. [3-6]. Atenolol and propranolol have been two agents frequently studied in the last decade in the control of this condition, and although no significant differences have been found between the two, there is much discussion at present about which drug to use [4-6]. Propranolol is a non-selective beta-blocker, which has been associated with several adverse effects, mainly in those with respiratory system disorders [4, 6]. Atenolol is a cardioselective beta-blocker, which can significantly affect patients with abnormalities of the cardiovascular system (mainly those with PHACES syndrome, who are at increased risk of heart defects) [4, 6]. Therefore, there is a need to study in depth and be very critical in the therapeutic plan of those patients with complicated infantile hemangiomas.

Ábarzúa-Araya et al [4] published in 2014 one of the first and most representative clinical trials to compare Atenolol and Propranolol in uncomplicated infantile hemangiomas. Although the authors found that Propranolol was more effective than Atenolol in terms of complete response (lesion resolution over time: 60% vs. 53.8%), these results were not significant ($p=0.68$). However, a very strong limitation was the study sample, only 23 patients [4]. Therefore, up to that date, the problem question remained

unresolved. Recently, in 2021, a trial was published with a more representative sample (337 participants), where Propranolol vs Atenolol was evaluated in the management of complicated infantile hemangiomas, whose main outcome was the response or non-response at 6 months [6]. The average age of the patients was 10 weeks and more than 70% were women. After 6 months, Propranolol and Atenolol response were 93.7% and 92.5%, respectively. The hemangioma activity score was similar at 1 week and 4 weeks after treatment (OR 1.03; 95% CI, 0.886 - 1.206) [6]. Although there were no significant differences in quality of life, ulcer healing time or rebound rate, the presence of adverse events was more frequent in the Propranolol group (70.0% vs. 44.4%). The complete response rate was similar at 24 months (82.1% vs 79.7%) [6]. Thus, it was concluded that Atenolol has an equally effective response as Propranolol, but is safer.

Only one month after the aforementioned trial was published, Muñoz-Garza et al [5], who evaluated the impact of Timolol vs. placebo in the early proliferative phase of uncomplicated infantile hemangioma, published another Spanish trial. Although there were only 69 patients, with an average age of 48 days, there was no evidence of superiority compared to placebo with respect to complete resolution at 24 weeks (42% vs. 36%, $p=0.37$), nor to variation in tumor size. The only favorable finding was an improvement in color and the absence of systemic adverse effects [5]. The most recent systematic review that has studied the effects of certain interventions in the management of infantile hemangiomas (laser, beta-blockers, radiation therapy and steroids) was done by Novoa et al [3] and published in 2018. The authors included 28 studies containing 1,728 participants, from various countries and ranging in age from 12 weeks to 13 years of age. Among the outcomes evaluated, the favorable result of propranolol vs. placebo on tumor volume reduction (RR 16.61; 95% CI, 4.22 - 65.34) and clearance (45.9%; 95% CI, 11.60 - 80.20) was highlighted [3]. No serious short- or long-term adverse effects were evident (RR 1.05; 95% CI, 0.33 - 3.39). However, the latter finding was not significant, and had a low level of quality. The use of topical Timolol (0.5% gel) vs. placebo showed a reduction in redness (RR 8.11; 95% CI, 1.09 - 60.09), with no adverse events reported [3]. When comparing topical Timolol vs. oral Propranolol with respect to the impact on tumor size, no significant differences were observed (RR 1.13; 95% CI, 0.64 - 1.97). However, effects that are more adverse were reported in the Propranolol group [3]. It should be noted that the authors reported that the quality of the outcomes evaluated and of the studies was moderate to low, the heterogeneity of the population studied was high (the age

range was very wide), and the available studies that have evaluated efficacy and safety between drugs are almost nonexistent [3].

At present, there are no clinical trials from Latin America or from low- and middle-income countries of similar regions. In order to comply with global health objectives [7], which establish the search for entities that affect early childhood and the control of the burden of pediatric diseases. It is necessary to encourage the design and systematization of data regarding the approach and outcome of infants and adolescents with complicated infantile hemangioma, to facilitate the resolution and ensure that there are no sequelae of any kind [8]. In addition, due to current barriers in low- and middle-income countries, such as timely access to specialized health care, it is imperative to design policies or groups that can reach hard-to-reach areas to identify or rule out these types of tumors, if they are mistaken for other conditions [8, 9]. Genomic studies are needed to characterize the behaviour of these tumors in regions where complicated infantile hemangiomas have not been studied in depth, to identify new therapeutic targets for a context-specific stratification of each population, according to their needs [9, 10]. These tumors, because they resolve at approximately 10 years of age in the vast majority of cases [1, 2], can entail a high catastrophic expense for a very long period of time, which can affect the development of the child and the functionality of his family.

To date, there is no sufficiently effective, efficient and safe therapeutic agent that is superior to other therapeutic tools designed for the management of complicated infantile hemangiomas. Although Propranolol has been shown to be superior to Atenolol in terms of efficacy, it is associated with numerous adverse events. Atenolol has been shown to be similar to Propranolol and other agents such as Timolol, with an acceptable safety profile. However, the current evidence is heterogeneous and of low quality. In this order of ideas, the therapeutic plan for complicated infantile hemangiomas should be multidisciplinary and personalized.

1. CONFLICT OF INTERESTS

The authors have no conflict of interest to declare. The authors declared that this study has received no financial support.

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