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REVIEW

Clinical and economic impact of surgery for treating infantile hemangiomas in the era of propranolol: overview of single-center experience from La Paz Hospital, Madrid

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Abstract

Propranolol has changed the management of infantile hemangiomas (IHs). We summarize the evolution of surgical treatment for IH at La Paz Children's Hospital (Madrid) in the era of propranolol, with a focus on hepatic IHs.

Retrospectively, we compared surgical treatment of IHs in children referred during the periods 2004–2009 and 2009–2014. Hepatic IH mortality rates before and after the introduction of propranolol therapy were evaluated specifically.

The majority of hemangiomas needing surgical excision were located on the head/face/scalp of female patients. Since the introduction of propranolol therapy, surgery for IH has decreased from about 60 to 6 procedures/year at our institution and no transplants for hepatic IH have been registered.

Conclusions: Surgical procedures for IH have decreased by about 90% at our institution since the introduction of propranolol treatment and hepatic IH have not needed liver transplantation. Referrals for surgery for IH are generally the consequence of absent or delayed propranolol treatment. Given the significant reduction in the number of surgical procedures, propranolol can be considered as having a strong economic and social impact.

What is Known:

- *The use of oral propranolol solution is currently considered as the treatment of choice in the management of infantile hemangiomas.*
- *Propranolol treatment achieves better outcomes and less side effects than systemic corticosteroids.*

What is New:

- *Social and financial impact of the significant reduction in the number of reconstructive surgical procedures and liver transplants due to the use of propranolol in tertiary health institutions remains to be analyzed.*

Keywords Beta-blockers · Facial hemangioma · Hepatic hemangioma · Infantile hemangioma · Propranolol · Surgery

Introduction

Infantile hemangioma is the most common benign tumor in children, with an incidence of about 5% [29] and a predominance in the female sex [8, 22, 24]. Infantile hemangiomas are usually not present at birth; the characteristic natural history includes a rapid proliferative phase during the first few months of life, followed by a slow proliferative phase, and then an involutional phase which can last until the fifth to the seventh year of life [22, 24]. At least 50% of hemangiomas lead to sequelae such as telangiectatic residual lesions, skin atrophy, or pigmentary changes [1, 2], and 10–15% develop complications such as ulceration, bleeding, or infection [22]. Although most infantile hemangiomas are cutaneous, they can also occur in the viscera, most commonly the liver [11].

Due to their usual spontaneous involution, only 10% of infantile hemangiomas require treatment; these are mainly those whose location could compromise a physical function (e.g., periorbital, perioral, nasal, or airway locations) or cause

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cosmetic disfigurement, large segmental hemangiomas, and complicated hemangiomas [8, 10, 13, 22, 30, 42].

Indications for the surgical treatment of infantile hemangiomas have decreased significantly due to improvements in pharmacological therapy. Following the discovery of the effectiveness of propranolol treatment by Léauté-Labrèze et al. in 2008 [20], systemic beta-blockers emerged as a first-line therapy [1, 8, 13], with a success rate of up to 98% in both cutaneous and visceral hemangiomas [10, 21, 27, 39, 43]. This has led to a reduction in the number of patients undergoing surgical resection or liver transplantation for hepatic infantile hemangioma [11]. Given the higher costs associated with surgery compared with pharmacological therapy for infantile hemangioma, treatment selection has financial as well as clinical implications.

La Paz Children's Hospital is the largest pediatric health institution in Spain, and the Vascular Anomalies Clinic is a reference center for the surgical removal of infantile hemangiomas. The hospital is also one of the busiest pediatric multivisceral transplant centers in the world, performing a mean of 25 abdominal transplants a year, including liver transplants.

This paper provides an overview of the evolution of surgical treatment for infantile hemangioma at La Paz Children's Hospital in the era of propranolol, considering two aspects. Firstly, we review retrospective findings from patients treated by surgery for infantile hemangiomas before, and in the era of, propranolol treatment. Secondly, we summarize the effect that the introduction of propranolol therapy has had on transplant surgery for hepatic infantile hemangiomas.

Surgical treatment of hemangiomas

Hemangiomas can be associated with functional and esthetic concerns, as well as complications such as ulceration [6]. Propranolol is effective in the treatment of infantile hemangiomas, including those located on the head, neck, and face [14, 21, 39, 44]. Surgery is only recommended as an option for patients with hemangiomas that have not responded to propranolol, have persistent ulceration, are at risk of obstructing or damaging vital organs, or will leave disfigurement after involution [1, 6, 8, 17].

The Vascular Anomalies Clinic at La Paz Children's Hospital in Madrid, Spain, is a reference center for the surgical removal of infantile hemangiomas. An analysis of children referred to the Vascular Anomalies Clinic was performed to evaluate surgical treatment for infantile hemangioma before and in the era of propranolol [41].

Retrospectively, we reviewed data for children seen at the Vascular Anomalies Clinic at La Paz Children's Hospital, Madrid, Spain, for surgical removal of an infantile hemangioma during the periods from 2004 to 2009 (before propranolol; group A) and from 2009 to 2014 (since propranolol; group B) (Table 1). Patients who required surgery to correct post-involutional sequelae were excluded because many of them were not given the option to be treated with propranolol before 2009. Epidemiological (gender) and clinical (location of IH) data were recorded and analyzed [41].

In the pre-propranolol period (group A), 304 patients (276 girls, 28 boys) were treated surgically for their hemangioma, whereas 45 children (38 girls, 7 boys) were referred for surgical treatment of IH in the propranolol period (group B). In group A, 72% of hemangiomas were located on the head (30% nose, 20% lips, and 22% forehead, cheek, and mandibular segments) while 28% of hemangiomas were located on other body areas (8% limbs, 8% perianal and external genitalia, and 12% trunk). In group B, hemangiomas were located on the head/face/scalp (80%; 9 periorbital, 10 nasal, 3 cheek, 7 lip, 4 ear, and 3 scalp) with the remainder located on other body areas (20%; 2 upper extremities, 1 lower extremities, 1 back, 3 thorax, and 2 abdomen) [41].

All patients in group A never received propranolol and failure of systemic corticosteroid administration in all of them resulted in surgical excision. Of the 45 patients included in group B, 22 patients were not offered any treatment as it was not considered necessary, 16 were treated with a systemic beta-blocker, 3 patients, despite being considered candidates for propranolol therapy, refused it for fear of potential adverse side effects, and the remaining 4 received alternative treatment [41].

Patients included in this retrospective analysis were mainly girls. The majority of hemangiomas requiring surgical excision were located on the head (face or scalp) [41]. Before the era of propranolol, failure of systemic corticosteroid therapy resulted in referral for surgical treatment of the hemangioma. As unresponsiveness to oral propranolol is rare [5], the absence of an appropriate indication for propranolol treatment, or a delay or refusal for initiating such a treatment, was the main current cause of surgical treatment of IH.

The institutional protocol for propranolol therapy for infantile hemangioma at the Vascular Anomalies Center at La Paz Children's Hospital considers as candidates those patients with potentially deforming hemangiomas, or hemangiomas that may compromise function or are likely to develop complications. In order to avoid a surgical solution for treating IH, these patients are reviewed weekly rather than monthly, as changes may be irreversible if aggressive proliferation occurs. Propranolol administration for the treatment of infantile hemangioma is usually initiated between the fourth and sixth week of life. When propranolol is introduced early, surgery is subsequently needed only for the few patients who show no response, estimated at less than 2% based on an analysis of data from 1175 patients in 79 published papers [10]. A large retrospective study involving 578 patients found a propranolol treatment failure rate of 1.9% among children aged under 2 months compared with 6.7% among children aged 2–8 months [44].

Table 1 Analysis of patients with cutaneous and liver hemangiomas in the pre- and post-propranolol era respectively

Surgery pre-propranolol	304 patients	304 received systemic corticosteroids	None received propranolol
Surgery post-propranolol	45 patients	4 received systemic corticosteroids	22 received propranolol
Liver hemangioma pre-propranolol	20 patients	3 transplants	4 deaths
Liver hemangioma post-propranolol	11 patients	No transplants	No deaths

Propranolol has dramatically changed the scope of management for patients with infantile hemangiomas. Since 2009, surgical procedures have been reduced by approximately 90% at our institution, from about 60 to 6 procedures a year. When reviewing our experience at La Paz Children's Hospital, the most important difference between the group of patients who underwent surgery for the treatment of infantile hemangioma before 2009 (approximately 60 per year) and the group of 45 patients operated on in the last 6 years (6 per year) is the indication for the surgical procedure. In the pre-propranolol era, the response to systemic steroids was not uniform and there was a higher rate of resistance and failure, leading to surgery. Since 2009, patients who have required surgery were not treated with propranolol early enough (i.e., they were not treated at the start of the proliferative phase of the hemangioma), and the delay in administration impeded full involution of the tumor.

Economic perspective

In addition to the clinical benefit for patients, the increased use of propranolol treatment has financial implications. Pharmacoeconomic studies specifically evaluating the effect of propranolol on the cost of treating infantile hemangioma have not been reported. However, surgical excision of birthmarks such as large hemangiomas typically costs US$15,000 or more (US cost estimate for patients not covered by health insurance) [7], whereas the average cost of propranolol treatment for non-visceral infantile hemangioma was estimated at US$2050 per patient in 2011 [34]. The direct medical costs associated with propranolol treatment for proliferating infantile hemangioma in Italy were estimated at €2399 in 2014 [32]. In Germany, the mean healthcare cost during the first year of life per infant treated for infantile hemangiomas (all body locations) was €10,550 in 2012 from a statutory health insurance perspective (i.e., including all treatment modalities; primary care, hospital, and dental costs; and any other healthcare costs) [38]. The majority of this (€8658) was due to hospitalization for invasive procedures or the initiation of pharmacotherapy (German centers often initiate propranolol during a 3-day hospital stay which allows the patient to be monitored), with drug costs accounting for another €986. Appropriate and early propranolol treatment would reduce the need for surgery and therefore the financial impact of infantile hemangiomas. Even considering that the cost of propranolol treatment can be higher in patients with aggressive tumors needing longer courses appropriate and early propranolol treatment would reduce the need for surgery and therefore the financial impact of infantile hemangiomas.

Liver hemangiomas

Hepatic infantile hemangiomas are the most common hepatic vascular tumor in the pediatric population [11]. The Children's Hospital of Philadelphia treated 26 patients with hepatic infantile hemangioma during a 10-year period from 1996 to 2007 [9], while the Children's Hospital Boston treated 121 patients in a 15-year period (1995–2010) [19] with another two patients identified between 2010 and 2012 [35]. Ankara Children's Hospital treated 13 patients with hepatic infantile hemangioma using propranolol over a 7-year period (2009–2016) [37]. Although they are benign tumors, they can be associated with hepatomegaly, arteriovenous shunting, abdominal compartment syndrome, hypothyroidism, bleeding, and cardiac failure [11]. The replacement of hepatic parenchyma with non-functioning tissue can occasionally cause acute liver failure in neonates, and massive hepatic hemangioma is a prominent cause of liver failure in this age group.

Hepatic infantile hemangioma has traditionally been considered a potentially life-threatening condition. For example, between 1958 and 1992, the Children's Hospital Los Angeles treated 30 children with hepatic hemangiomas, of whom six died, representing a 20% mortality rate [15]. Between 1969 and 1996 at the Boston Children's Hospital, the following mortality rates were reported after treatment of 39 children with liver hemangiomas: resection of solitary lesions 20% (2/10), embolization 43% (3/7), corticosteroids 30% (3/10), and interferon alfa-2a 15% (2/13) [4]. Among the treatment options available at that time, steroids, vincristine, interferon, and cyclophosphamide were not uniformly successful, and liver transplantation emerged as the final therapeutic option for children in whom medical treatment had failed and/or the hemangioma was too large or multifocal for primary resection [23, 26, 36]. Since 2008, propranolol has become the first-line agent for medical therapy of patients with infantile

hemangioma and has been shown to be effective in many patients with hepatic hemangioma [16, 25, 28].

At our center, La Paz Children's Hospital, Madrid, the mean time on the waiting list for liver transplantation over the last 10 years was 5 months. In the period from 1995 to 2005, 20 patients with hepatic infantile hemangioma were managed at our center, of whom three underwent liver transplantation and four died while on the transplant waiting list. Starting in June 2008, every child seen at the hospital with hepatic hemangioma has been treated with propranolol, and since then, no transplants for this indication have been registered at our institution and no deaths have been recorded.

The total number of liver transplant procedures being performed (for any indication) is growing progressively. For example, in Spain, the number of procedures has increased from 495 in 1993 to 1162 in 2015, which represents the highest rate in the world (24.9 liver transplants per million inhabitants) [31]. In 2015, 107 children were registered on the waiting list for liver transplantation. However, there is evidence that the number of transplants being performed for infantile hemangioma has decreased since 2008, when propranolol started being used in the treatment of such patients. The United Network for Organ Sharing (UNOS) database recorded that a total of 8047 children under 1 year of age underwent liver transplantation between 1989 and 2008, of whom 35 received transplants because of hemangioma. In contrast, between 2009 and 2017, among 2672 children aged less than 1 year who underwent liver transplantation, none had a diagnosis of hemangioma [40]. The Pediatric Liver Unresectable Tumor Observatory (PLUTO) is a registry developed by an international collaboration of the Liver Tumors Strategy Group. In 2006, two patients with liver hemangioma were registered in PLUTO as being on a waiting list for liver transplantation, whereas in the period 2008–2015, no hemangioma patients were registered [33].

Economic perspective

Liver transplantation is an expensive procedure. The estimated average billed charges per liver transplant in the USA in 2014 was US$739,100 [3], while a German study published in 2017 reported a median total treatment cost of €144,424 per liver transplant for the period from entry to the waiting list until 3 years post-transplantation [12]. In Japan, the total treatment cost per liver transplant in 2010 was 4.95 million yen for the month of transplantation and 7.75 million yen if the subsequent 2 months were also included [18].

Where possible, the use of alternative effective treatment options that are less expensive than liver transplantation would be financially beneficial for healthcare systems. No pharmacoeconomic studies specifically evaluating treatments for infantile hepatic hemangioma have been published. However, the cost of treatment with propranolol is considerably lower than the cost of liver transplantation. An Italian study estimated the direct medical costs associated with propranolol treatment for proliferating infantile hemangioma (not specified further) were €2399 in 2014 [32], and a US study reported that the average cost of propranolol per treated patient with non-visceral infantile hemangioma was US$205 in 2011, based on an average treatment duration of 7.9 months [34].

As propranolol treatment has undoubtedly led to a reduction in the number of liver transplantation procedures being performed for hepatic hemangioma around the world, it can be expected to also have had a substantial impact on the financial aspects of the management of this disease.

Conclusions

The use of propranolol to treat patients with infantile hemangiomas has had a substantial impact on the management of this disorder, leading to a notable reduction (by about 90%) in the need for surgical treatment. More particularly, it has dramatically reduced the number of liver transplantation procedures and deaths associated with hepatic hemangiomas. Given the significant reduction in the number of surgical treatments, propranolol can be considered as having a strong economic and social impact by decreasing costs related to hospital stay and by avoiding unnecessary scars and postsurgical esthetic and functional sequelae with a significant reduction in the burden of disease on parents of children requiring systemic treatment.

Patients, particularly girls, with a facial infantile hemangioma should be reviewed weekly for 4–6 weeks. Guidelines should emphasize the need for early pharmacological treatment of infantile hemangiomas that would reduce the need for subsequent surgical treatment.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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