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Efficacy of Oral Propranolol and Laser Therapy for Infantile Hemangioma

Kenji Miyata[1)], Toshinori Hori[1)], Yasuto Shimomura[1)], Mami Tanaka[2)], Ayako Nagata[2)], Kazuhisa Yokoo[2)], Kenta Murotani[3)4)], Koji Nishihori[5)] and Akihisa Okumura[1)]

[1)] *Department of Pediatrics, Aichi Medical University, Nagakute, Japan*
[2)] *Department of Plastic Surgery, Aichi Medical University, Nagakute, Japan*
[3)] *Division of Biostatistics, Clinical Research Center, Aichi Medical University, Nagakute, Japan*
[4)] *Biostatistics Center, Kurume University, Kurume, Japan*
[5)] *Nishihori Plastic Surgery, Nagoya, Japan*

Purpose: Despite its benign and self-limited nature, infantile hemangioma can cause complications such as ulceration and permanent disfigurement. Oral propranolol has become the treatment of choice for infantile hemangioma, based on an efficacy comparable to that of laser therapy. The aim of this study was to compare the efficacy and safety of oral propranolol and long-pulsed dye laser in infantile hemangioma.

Materials and Methods: This was a single-center retrospective study including 143 patients with infantile hemangioma. The treatment option was chosen by the plastic surgeon. Oral propranolol was started at a dose of 0.5 mg/kg/day, with a maintenance dose of 2.0 mg/kg/day. The clinical response was classified as excellent, good, moderate or poor according to a four-point scale system based on a reduction in lesion volume, and changes in lesion color and surface tension.

Results: Forty-two children were treated with oral propranolol and 101 with long-pulsed dye laser. Treatment efficacy 12 months after treatment was 81% and 80%, respectively, and did not differ by sex, age, or infantile hemangioma type or site. Three months after the initiation of therapy, the efficacy rate was higher in the oral propranolol group than in the long-pulsed dye laser group (50% vs. 30%, $P=0.034$). There was no difference in therapeutic efficacy between children treated with oral propranolol alone and those treated with a combination of oral propranolol and adjunctive long-pulsed dye laser. Cumulative efficacy was higher in the oral propranolol group than in the long-pulsed dye laser group at 6 months in the subset of patients with superficial infantile hemangioma, and at 3 and 6 months in patients who started therapy before 3 months of age.

Conclusion: Oral propranolol and long-pulsed dye laser were equally effective in the treatment of infantile hemangioma. However, the efficacy of oral propranolol appeared earlier within the first few months after treatment initiation.

Key words: Infantile hemangioma, Oral propranolol, Long-pulsed dye laser

INTRODUCTION

Infantile hemangioma (IH) is the most common benign tumor of the soft tissue in childhood. The estimated prevalence in the general population is 10–12%, and ~1% in Japanese children[1)2)]. IH is frequently located in the head

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and neck, trunk, and extremities, but it can occur in any part of the body[3)4)]. IH is often seen in premature infants[5)6)] and ~30% of IHs are already present at birth[7)]. In most infants, spontaneous regression occurs over several months to several years, but in 10–12% of infants IH may be complicated by bleeding, ulceration, infection, and compromise of adjacent vital structures. Even in IHs that regress over time, in some cases there is residual redundant fibrofatty tissue, scarring, residual telangiectasia, or pigment changes. Although IH is medically insignificant in the vast majority of affected infants, significant parental concern often arises regarding the psychosocial burden imposed by an IH, and its effects on the child's appearance. Therefore, an effective and safe treatment for IH in infants is desirable[8)].

Propranolol, a nonselective β-blocker antagonizing both β1 and β2 receptors, has attracted the attention of clinicians involved in the treatment of infants with IH. Although the mechanism underlying the effect of propranolol on IH is unclear, it has been shown to decrease the expression of vascular endothelial growth factor and fibroblast growth factor, thus inducing apoptosis in capillary endothelial cells[9)]. The efficacy of oral propranolol (OP) in IH was first reported in 2008 and excellent outcome and safety of OP in infants with IH has been demonstrated[10)11)]. In Japan, laser therapy for IH is common but OP is becoming the treatment of choice. However, few studies have compared the efficacy of OP and laser therapy. Therefore, in this study, we compared the efficacy and safety of these two forms of treatment in infants with IH.

MATERIALS AND METHODS

The study was conducted as a collaboration between the Departments of Pediatrics and Plastic Surgery, Aichi Medical University. Children with IH who were referred to the hospital from April 2012 and August 2017 were enrolled. IH was diagnosed based on the medical history and physical examination according to the classification of vascular anomalies published by the International Society for the Study of Vascular Anomalies (ISSVA)[12)]. In most cases, children with IH were first referred to the Department of Plastic Surgery, where they were evaluated by a plastic surgeon who determined the treatment option: long-pulsed dye laser (LPDL) or OP. Children allocated to the latter group were referred to the Department of Pediatrics, where a pediatrician evaluated the child's eligibility for OP therapy before its initiation. Children with congestive cardiac heart disease, bradycardia, asthma, or obstructive pulmonary disease were excluded from the study. Some children treated with OP also received LPDL when deemed necessary by the plastic surgeon. Written informed consent was obtained from the parents of all children included in the study. This study was approved by the Ethics Committee of Aichi Medical University Hospital.

IH was categorized as superficial, deep, or mixed. The superficial type is the most common and consists of a bright red papule, nodule, or plaque raised above apparently normal skin. The deep type is typically a raised, skin-colored nodule that often has a bluish hue, with or without a central telangiectatic patch. The mixed type comprises both superficial and deep components (Fig. 1).

OP protocol

Before the start of OP, a chest radiograph and electrocardiogram were obtained and laboratory tests were performed. OP was started at a dose of 0.5 mg/kg/day and was increased in increments of 0.5 mg/kg/day per day when no

Fig. 1. Types of infantile hemangioma (IH) and response to treatment
A: Superficial, B: deep (surrounded by a broken line), and C: mixed types of IH.
D and E. Example of effective treatment of IH before (D) and after (E) treatment with a long-pulsed dye laser on the forehead.
F and G. Example of ineffective treatment of IH before (F) and after (G) treatment with oral propranolol and a long-pulsed dye laser on the upper limb.

adverse effects were observed. The maintenance dose of OP was 2.0 mg/kg/day. For the first 5 days of treatment, blood pressure, heart rate, and blood glucose level were monitored every 8 h and an electrocardiogram was recorded daily. Follow-up was performed at our outpatient pediatric clinic every 1–3 months, and the dose of propranolol was adjusted for weight gain. OP was usually adopted for children with deep and mixed types of IH, but it was also used in children with superficial IH when parents were concerned about cosmetic and/or functional problems potentially associated with laser therapy.

LPDL protocol

LPDL was performed with a wavelength of 595 nm and pulse duration of 1.5–6.0 ms, a spot size of 7 mm, and an energy fluence of 8.0–11.5 J/cm^2. Treatment was repeated every 4–12 weeks (median, three treatments) depending on the rate of IH proliferation, and was discontinued when the IH cleared or no longer proliferated. LPDL was usually adopted in children with superficial- or mixed-type IH.

Clinical evaluation

Data on the sex of the patient, age at the start of therapy, duration of therapy, type and site of IH, and adverse events were collected. Digital photographs of IH were taken at enrollment and at each follow-up visit and used together with the clinical findings to evaluate the response to treatment. A consensus was reached among the pediatricians (KM and TH) and the plastic surgeon (KY) using a four-point classification system pertaining to the decrease in tumor size [13]: I, by ≤25%; II, by 26–50%; III, by 51–75%; and IV, by 76–100%. The change in tumor color was scored as 0 (bright red) or 1 (lighter or dark), and the change in surface tension as 0 (hard) or 1(soft, associated with shrinkage or flattening). A sum score of 5 was considered to indicate an excellent response; 4, a good response; 3, a moderate response; and <3, a poor response. Treatment was judged as effective when the response was good or excellent (Fig. 1); otherwise, it was judged as ineffective (Fig. 1). The efficacy of treatment was determined every 3 months after the initiation of therapy, and the final efficacy at 12 months after therapy initiation.

Statistical analysis

The cumulative efficacy rates of therapy were compared using the chi-squared test every 3 months after the initiation of therapy. The characteristics of the children treated with LPDL versus OP were compared using the chi-square and Mann-Whitney U tests for categorical and numerical variables, respectively. Categorical variables among three or more groups were compared as follows. First, chi-square tests were conducted to identify significant differences between the groups. If a difference was significant, residual analysis was performed. A p-value <0.05 was considered to indicate statistical significance. All statistical analyses were performed using EZR software (ver. 1.34; available at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html)[14].

RESULTS

The study population consisted of 143 children (102 females, 73%) with IH; 42 (29%) were assigned to OP treatment and 101 (71%) to LPDL treatment. Steroid was used only in one patient treated with OP. Adjunctive LPDL treatment was performed in 31 of the 42 children treated with OP. The characteristics of the patients are shown in Table 1. The median age at the start of therapy was 3 months (range: 1–24 months). The two groups did not differ significantly with respect to sex distribution or age at the start of therapy. The duration of therapy was longer in the OP than in the LPDL group, with a median of 15 months (range: 5–30 months) and 7 months (range: 0–23 months), respectively. The type and site of IH differed between the two groups; the superficial type was less frequent, and the deep and mixed types were more frequent, in OP than in LPDL patients. Facial lesions were more frequent, and lesions of the trunk and extremity less frequent, in the OP than in the LPDL group.

The efficacy of the two types of therapy 12 months after treatment initiation did not significantly differ (81% in the OP group and 80% in the LPDL group; Table 2). There was also no difference in treatment efficacy after subdividing the groups according to sex, age, or type or site of IH.

Fig. 2 shows the cumulative efficacy of OP (42 patients) and LPDL (101 patients) every 3 months after therapy initiation. Up until 6 months after the initiation of therapy, the cumulative efficacy was higher in OP than in LPDL patients (50% vs. 30% at 3 months, $P=0.034$, and 76% vs. 54% at 6 months, $P=0.049$) whereas at 9, 12 months after therapy initiation the differences were not signifi-

Table 1. Patient characteristics

	OP (N=42)	LPDL (N=101)	P value
Gender (M:F)	10:32	31:70	0.41
Age at the start of therapy (months)*	3 (1–11)	3 (1–24)	0.88
Duration of therapy (months)*	15 (5–30)	7 (0–23)	<0.001
Type of infantile hemangioma			<0.001*2
Superficial	24 (57%)	98 (97%)	
Deep	4 (10%)	0	
Mixed	14 (33%)	3 (3%)	
Site of infantile hemangioma			<0.001*3
Face	20 (48%)	21 (21%)	
Head and neck	9 (21%)	12 (12%)	
Trunk	5 (12%)	36 (36%)	
Extremity	4 (10%)	25 (25%)	
Multiple	4 (10%)	7 (7%)	

*: Data are shown as median (range).
*2: $p<0.001$ in superficial; $P=0.0017$ in Deep; $p<0.001$ in mixed.
*3: $p<0.0012$ in face; $P=0.0042$ in trunk; $p<0.019$ in extremity.

Table 2. Efficacy 12 months after the treatment

Efficacy	OP (N=42)	LPDL (N=101)	P value
Total	34/42 (81%)	81/101 (80%)	>0.99
Gender			
Male	8/10 (80%)	26/31 (84%)	0.78
Female	26/32 (81%)	55/70 (79%)	0.76
Age at the start of therapy			
≤3 months	19/23 (83%)	40/52 (77%)	0.58
>3 months	15/19 (79%)	41/49 (84%)	0.65
Type of infantile hemangioma			
Superficial	21/24 (88%)	79/98 (81%)	0.43
Deep	4/4 (100%)	0	Not assessed
Mixed	9/14 (64%)	2/3 (67%)	0.94
Site of infantile hemangioma			
Face	15/20 (75%)	14/21 (67%)	0.56
Head and neck	9/9 (100%)	9/12 (75%)	0.11
Trunk	4/5 (80%)	29/36 (81%)	0.98
Extremity	3/4 (75%)	23/25 (92%)	0.30
Multiple	3/4 (75%)	6/7 (86%)	0.66

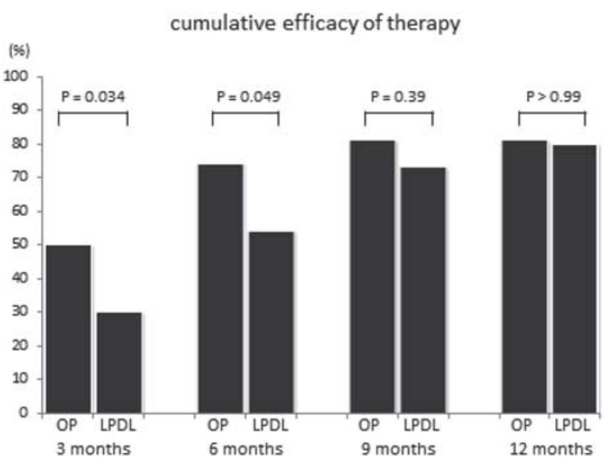

Fig. 2. Cumulative efficacy of LPDL and OP according to the duration of therapy

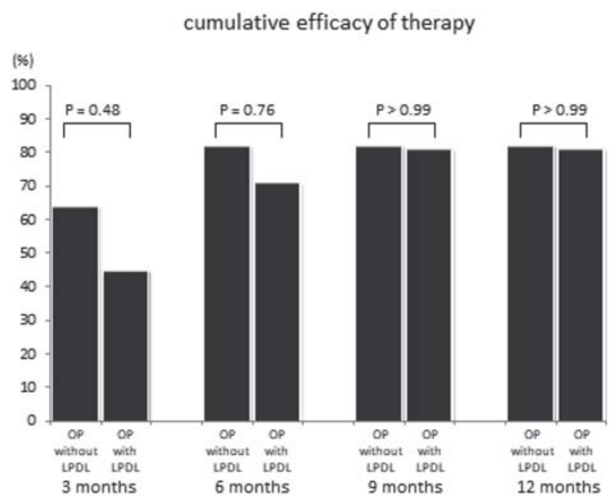

Fig. 3. Cumulative efficacy of OP without LPDL and OP with LPDL according to the duration of therapy

cant. The efficacy of OP in the presence or absence of adjunctive LPDL was also determined (Fig. 3). The efficacy of OP (11 patients) vs. OP+LPDL (31 patients) did not differ at any time. We then compared the cumulative efficacy of OP (24 patients) and LPDL (98 patients) only in patients with superficial type IH (Fig. 4), in which LPDL is the most common form of therapy. At 3 months after therapy initiation, the efficacy was higher in OP than in LPDL patients, but the difference was not significant (50% vs. 31%, P=0.12). At 6 months after the initiation of therapy, the cumulative efficacy was higher in OP than in LPDL patients (83% vs. 55%, P=0.021). Thereafter, there was no

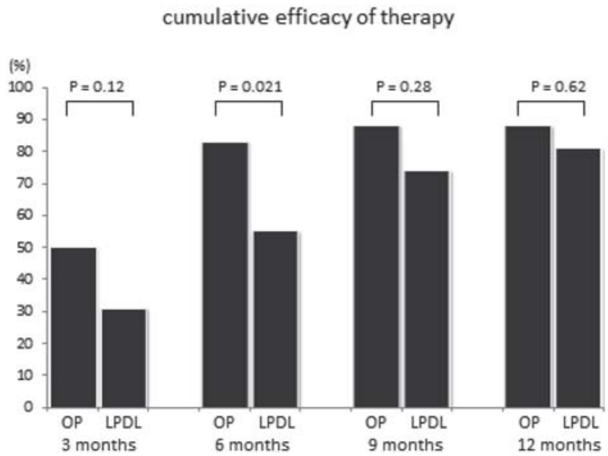

Fig. 4. Cumulative efficacy of LPDL and OP according to the duration of therapy among patients with superficial type

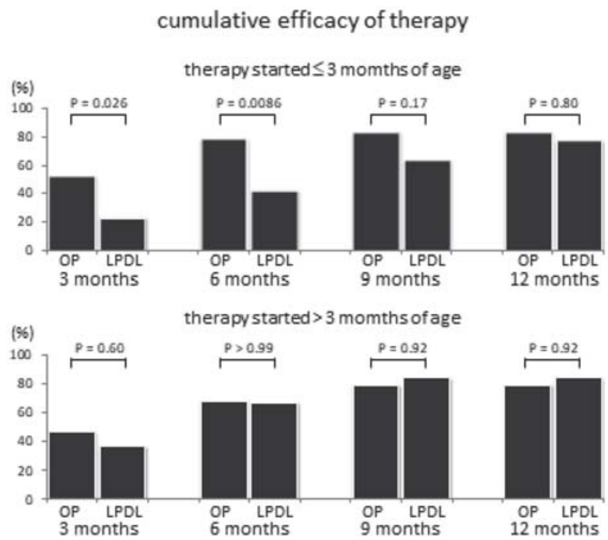

Fig. 5. Cumulative efficacy of LPDL and OP according to the duration of therapy among patients who started therapy by 3 months of age and beyond 3 months of age

significant difference in the cumulative efficacies of the two treatments.

We also analyzed the difference in efficacy according to age at the start of therapy (Fig. 5). In patients who started therapy before 3 months of age, the cumulative efficacy was higher in those treated with OP (23 patients) than with LPDL (52 patients) up until 6 months after the initiation of therapy (52% vs. 23% at 3 months, P=0.026, and 78% vs. 42% at 6 months, P=0.0086). Thereafter, the cumulative efficacy of OP vs. LPDL did not differ significantly. By contrast, in patients who started therapy later than 3 months of age, the difference in the cumulative efficacy of OP (19 patients) vs. LPDL (49 patients) was not significant.

Regarding adverse effects, 11 children (26%) treated with OP had mild and transient elevations of liver function, as determined by laboratory tests. In all of these patients, the values returned to within the normal range by the end of study. No children treated with OP developed hypotension, bradycardia, or hypoglycemia. Scarring, erosion, or ulceration was not observed in any child during this study.

DISCUSSION

This study compared the efficacy of OP and LPDL in the treatment of IH. The two therapies were equally effective at 12 months after initiation, with >80% of the treated children responding to each treatment type. However, at 3 and 6 months after the initiation of therapy, OP was more effective than LPDL, suggesting rapid onset of action.

Indeed, the efficacy of OP in our cohort was comparable to that determined in previous studies. Within our cohort of pediatric IH patients, OP was effective in 81% of cases by 12 months after the initiation of therapy. The efficacy of propranolol in IH was first described in 2008, in a study showing marked improvement in 11 children[10]. The efficacy and safety of OP were established in a randomized, controlled trial[15] in which 460 infants were randomly assigned to receive placebo or one of four propranolol regimens. Improvement was seen in 88% of infants who received a regimen of 3 mg propranolol/kg/day for 6 months. In the systemic review of Marqueling et al., which included 1,264 pediatric patients with IH, clinical improvement occurred in 82–100% of those treated with OP[16]. Other authors reported OP efficacy rates of 76–78% in the treatment of IH[17)18]. These findings support OP as a highly effective therapy, including as a standard treatment, for infants with IH.

Our study also revealed faster onset of action of OP than LPDL. IHs reach 80% of their maximal size by the time the infant is 3 months of age and a large majority of the tumors cease growth by 5 months of age[1)19]. The use of OP to effectively treat an IH before it reaches its maximal size seems to result in a better outcome. Other observational studies have also shown rapid efficacy of OP for IH. Baetz et al. described a patient with a severe IH treated with OP over 5.5 months[20]. A few weeks after treatment initiation, the IH was significantly reduced in size and had regressed almost completely. Rotter et al. reported a retrospective study of 19 patients treated with 2 mg OP/kg/day. A color change and size reduction in the tumors occurred during the first 3 months[21]. The early, rapid reduction of IH by OP can be attributed to its immediate vasoconstrictive effects via the β2-adrenergic receptors on IH endothelial cells, and a decrease in vasodilatory nitric oxide release[22)23]. However, Ji Y et al. reported that propranolol may exert its pharmacological effect by evoking pericyte-mediated vasoconstriction, without impacting hemangioma endothelial cells[24]. However, as the more rapid onset of action of OP versus laser therapy has yet to be investigated specifically, further studies are needed to validate this finding. The rapid reduction of IH will be helpful in reducing the level of concern of parents of children with IH.

The efficacy of a combination of OP and laser therapy for IH has also been evaluated[25)~27)], with several authors reporting that combination therapy is more effective than OP alone. In the study of Reddy et al., in patients with IH treated concurrently with OP and PDL, near-complete clearance was achieved after fewer days of propranolol treatment and complete clearance was finally achieved in 6 of 12 infants; meanwhile, when OP was followed by PDL, clearance occurred in 2 of 5 patients, while in those treated with OP alone clearance was seen in 1 of 8 patients[25]. Furuta et al. compared the therapeutic efficacy of laser, OP, and a combination of OP and laser treatment. They concluded that within 3 months of the initiation of treatment, combination therapy was most effective in terms of both color-fading and tumor size reduction[27]. However, in our study, the efficacy of OP alone was similar to that of a combination of OP and LPDL at all measured time points. The difference in these results may have been due to the small number of children treated with OP alone in our study. Further studies are necessary to determine whether a combination of OP and laser therapy is superior to OP alone for treating infants with IH.

LPDL is appropriate for the treatment of superficial IH but is usually unsuitable for deep or mixed IH. In this study, a comparison of the efficacy of therapy exclusively in patients with superficial IH showed the faster efficacy of OP in this subset of patients. This finding is noteworthy because in patients with superficial IH, parents are concerned about their child's risk of serious cosmetic problems, and OP is a form of therapy whose potential efficacy can be easily explained to parents and caregivers. Thus, parents will be encouraged by the rapid reduction of IH, even if the final efficacy of OP does not differ from that of LPDL. Indeed, the rapid efficacy of OP offers an advantage when considering the choice of therapy for IH.

The rapid efficacy of OP was observed in patients who started treatment by 3 months of age, but not in those who started therapy thereafter. The reason for this relationship between age at the start of the therapy and OP efficacy is not understood. El Hachem et al. compared the safety and efficacy of OP for IH patients before 5 weeks and after 5 months of age[28]. The authors reported acceptable safety and efficacy profiles of OP in both age groups. Considering that IHs reach 80% of their maximal size by 3 months after birth, treatment before this age may be rational, assuming that the chosen therapy can be safety used in young infants. The appropriate timing of OP initiation merits further study.

OP is considered safe for infants with IH, although the known adverse effects of propranolol include bronchospasm, hypoglycemia, mood disturbances, bradycardia, and hypotension[29]. Buckmiller et al. reported no adverse effects related to OP when used to treat tracheal IH causing stridor and airway compromise. Complete remission was achieved within 6 weeks from the start of OP (2 mg/kg/day)[30]. Tian et al. reported a retrospective study of 31 patients with IH in the proliferative phase. There were also no adverse effects of OP treatment (2 mg/kg/day) in that study, nor were any seen at follow-up[17]. In a nationwide claims database survey performed in France, standardized morbidity ratios for respiratory or metabolic events were not significantly higher even in "nonhealthy" children treated with OP[31]. In our patients, a transient elevation of liver function tests was observed in 26% of those treated with OP, but none of the OP-treated children developed adverse effects, such as hypotension, bradycardia, or hypoglycemia. These results suggested that OP will be well-tolerated in infants with IH.

There were several limitations to our study. First, the number of patients was too small to allow a detailed evalution of the differences in efficacy according to patient age and IH site. Dong et al. conducted a retrospective study of 169 patients with IH of the head and neck region who were treated with OP. Significant effects of age at treatment initiation and IH type on outcome were noted[32]. To explore the prognostic factors affecting the therapeutic effects of OP in IH, a larger number of patients will be required in future studies. Second, in our non-randomized, retrospective study, a majority of patients with superficial type IH were treated with LPDL. Thus, the selection of treatment was biased according to IH type and site. To compare the efficacy of different therapies, randomized prospective studies are needed. However, laser therapy is not considered suitable for deep IH. Thus, future studies will need to limit the type or site of IH. Because in our study LPDL was used additionally in a majority of the children treated with OP, strict evaluation of the efficacy of OP was difficult. Clarification of the efficacy of OP will require comparisons of children treated with OP alone, with no additional laser treatment, and with laser therapy alone. Also, the long-term outcome in our patients is unknown, because the follow-up period was short. Final determination of the efficacy of any therapy should be based on the outcome after several years. Finally, the evaluation of the efficacy of treatment in this study was only based on digital photographs. In order to achieve more precise evaluation, the imaging evaluation using MRI and/or ultrasonography should be incorporated.

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