Results of Laser Photocoagulation Therapy for Retinopathy of Prematurity and Additional Treatment Requirements

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ABSTRACT

Purpose: The objective of the study is to assess the efficiency of treatment, additional treatment requirements and results of additional treatments in infants who underwent laser photocoagulation (LP) due to retinopathy of prematurity (ROP).

Materials and Methods: This two-center, retrospective trial evaluated the treatment results of preterm infants who underwent LP for ROP between 2013 and 2019 and who were also followed for at least 1 year following LP.

Results: Four hundred thirty-seven eyes of 225 infants were included in the study. Of the eyes treated with LP, 284 had type 1 ROP, 129 had type 2 ROP, and the remaining 24 eyes had aggressive posterior retinopathy of prematurity (APROP). After the initial LP, manifestations of ROP regressed completely in 397 (90.8%) eyes, whereas for 40 eyes (9.2%), additional treatment was required. Of these infants, 18 (45%) eyes underwent rescue intravitreal bevacizumab (IVB), while LP was applied at the posterior ridge of 16 (40%) eyes, and additional LP was applied in 6 (15%) eyes. Fourteen (58.3%) eyes with APROP and 26 (9.2%) eyes with type 1 ROP required additional treatments, and the difference between them was statistically significant ($p<0.001$). After all follow-up and treatments, an unfavourable anatomic outcome was observed in 4 eyes (0.9%) at a corrected age of one year.

Conclusion: Near-confluent LP is an efficient treatment, in particular for infants with type 1 and type 2 ROP. However, the requirement of additional treatment following the initial LP is greater in infants with APROP.

Keywords: Aggressive posterior retinopathy of prematurity (APROP), Type 1 retinopathy of prematurity (ROP), Type 2 retinopathy of prematurity, Laser photocoagulation (LP)**.**

INTRODUCTION

In spite of the effective screening and treatment routines, retinopathy of prematurity (ROP), which was described as 'retrolental fibroplasia' for the first time by Terry, remains a primary cause of childhood blindness in both developed and developing countries[1,2]. Furthermore, the incidence rate of ROP has risen remarkably, particularly in developing countries, due to advances in neonatal intensive care units (NICU) and increased birth rates[3].

Vaso-obliteration due to hyperoxia and subsequent hypoxia is considered to be possibly responsible for the development of neovascularization, though the pathogenesis of the illness cannot yet be precisely revealed[4]. If the disease is not treated in its initial stages, vision loss occurs due to macular traction and retinal detachment in the later stages[5].

In order to prevent permanent blindness, which might be caused by ROP, early treatment of the avascular retina is required[6,7]. Peripheral retinal ablation through a diode or argon laser is the gold standard treatment option for the treatment of ROP. Recent research has revealed that 10% of infants could still have unfavourable outcomes, though laser therapy is generally beneficial[7]. Hence, there has recently been an increase in the use of anti-vascular endothelial growth factor (VEGF) agents. In the prospective randomised controlled trial, entitled "The Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity (BEAT-ROP)", intravitreal bevacizumab

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Received: 14.01.2021
Accepted: 26.06.2021
Ret-Vit 2021; 325-332
DOİ: 10.37845/ret.vit.2021.30.57

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(IVB) and conventional laser photocoagulation (LP) treatment was analysed, and better effectiveness was reported in comparison with the LP, particularly in the infants with zone 1 ROP[8]. Moreover, many clinicians prefer to perform IVB injection combined with LP or prior to surgery to improve post-surgical outcomes[9,10].

The current study will evaluate the results of the LP that had been performed for the treatment of ROP at two tertiary care centres between 2013 and 2019. Another objective of this study is to assess the efficacy of LP applied to the ridge posterior and IVB therapy applied as a rescue therapy following failure of initial LP.

METHODS

Study design and population

This two-center, non-randomised, retrospective trial was conducted in the Gaziantep Children's Hospital and ophthalmology department of Kahramanmaras Sutcu Imam University Medical Faculty, which are referral centres for the screening and treatment of ROP. Included in the research were the infants who had been followed up and treated in the NICU of these two centres and the infants who had been referred for treatment from various NICUs in the district (public hospitals, private hospitals, university hospitals, and training and research hospitals). The study was approved by the local ethics committee of Kahramanmaras Sutcu Imam University Medical Faculty (2020/05-15) and was performed in compliance with the principles of the Helsinki Declaration. An informed consent form was obtained from the parents of the infants before the treatment.

Retrospective demographic and clinical data of the infants who had been treated with LP between 2013 and 2019 were examined. An information form, which includes data regarding the gestational age (GA), birth weight (BW), gender, ROP type (type 1 ROP, type 2 ROP or APROP), zone and the time of treatment according to postmenstrual age (PMA) of all infants who were included in the study, was filled. Moreover, additional treatment requirements (additional LP, LP to the ridge posterior or administration of rescue IVB), complications and anatomical outcomes post-LP treatment were analysed. Dragging of the optic disc and macula, tractional and persistent non-tractional membranes located in the posterior pole or retinal periphery, partial or total retinal detachment were considered unfavourable anatomic outcomes[11]. İnfants who had at least 1-year follow-up after the LP therapy were included in the study. Infants whose clinical and demographic data were inadequate, infants who underwent LP due to stage 4 ROP, and infants who received laser therapy after anti-VEGF medication were excluded from the study.

Ophthalmic Examinations and Treatment Modalities

All of the infants in these two referral centres were screened in line with the screening criteria appropriate for our country (all of the infants whose GA≤32 weeks or BW≤1500 grams, and those whose GA>32 weeks or BW>1500 g and also received palliative care for cardiopulmonary or preterm infants who were considered to be at risk for ROP progress by the clinician following the infants)[12]. Eye examinations of premature infants were conducted by experienced ophthalmologists (retinal specialists) using an indirect ophthalmoscope and scleral depressor at 4 weeks postpartum (for infants born <27 weeks postnatal 31st week) based on GA. The stage, location zone and plus disease findings of the ROP were categorised based on the guidelines of the International Classification of ROP (ICROP)[13]. Subsequent examinations and treatments were planned in compliance with the recommendations for the Early Treatment of ROP (ETROP)[11]. Therapy was performed in cases of type 1 ROP (zone I any ROP with plus disease, zone I stage 3 ROP with or without plus disease, Zone II stage 2 ROP with plus disease) and APROP development (in zone I or posterior zone II, increased dilation and tortuosity of the posterior pole vessels in all quadrants out of proportion to the peripheral retinopathy with flat network of shunts within retina or at the junction between vascular and avascular retina)[11,13].

In our centers where the study was conducted, infants with type 2 ROP (zone II stage 3 without plus disease and zone I stage 1 or 2 without plus disease) were followed up closely (1 time in 3 to 5 days) in accordance with ETROP recommendations, and infants with progression to type 1 ROP were applied LP therapy[11]. In addition, LP was applied to cases with persistent stage 3 ROP in zone 2 with marked vascular tortuosity despite close follow-up for at least 1 month, and cases with type 2 ROP structural changes such as fibrovascular membrane extending to the vitreous and traction causing flattening of the temporal arcuates were observed and cases with type 2 ROP who developed preretinal hemorrhage and/or intravitreal hemorrhage during follow-ups.

In addition to these, infants were referred to our study centers for ROP treatment from various NICUs both in our own regions and in the eastern and southeastern anatolia region, and due to the geographic location of these centers (because of their border with Syria), many refugee cases were screened and followed up. For this reason, LP was

applied to the cases with type 2 ROP (zone II stage 3 without plus disease) who could not comply with close follow-ups due to referral from distant cities after the NICU discharge and to the refugees who had to return to their countries.

In our centres, anti-VEGF agents are administered as the primary medication, in line with the approval of the family as well as based on the results obtained from the BEAT ROP[8] study, particularly in cases located at the posterior zone (zone 1 and posterior zone 2) and infants with APROP. Meanwhile, LP was applied as the primary treatment for type 1 and type 2 ROP cases located in zone 2. In addition, LP treatment was applied primarily to infants with APROP and type 1 ROP located in the posterior zone and whose families did not consent to anti-VEGF medication. Following the LP treatment, in case of failure or recurrence of ROP, families were informed elaborately, and additional LP, LP application to the ridge posterior or rescue anti-VEGF medications were performed. Cases that progressed or developed retinal detachment despite all interventions were referred to advanced health care centres for vitroretinal surgery.

Prior to the LP, both eyes of the infants were dilated with tropicamide at 0.5% and phenylephrine hydrochloride at 2.5% 3 times with intervals of 5 minutes. The treatment was administered after ensuring topical anaesthesia with a single drop of proparacaine hydrochloride at 0.5%, and through monitoring vital parameters under sedation with ketamine hydrochloride or midazolam. Treatments were performed in the neonatal intensive care unit under the supervision of a team of specialist physicians. LP was conducted through an 810 nm head-mounted diode laser (Iridex; Oculight SL, Mountainview, CA, USA) with a near-confluent pattern from the vascularised retinal region to the avascular retina in all quadrants at 360 degrees. Drops of antibiotics and steroids were administered daily every 4 hours, which lasted throughout one week following the procedure of LP.

Weekly follow-ups were conducted throughout the first month after LP therapy. The plus disease findings and complete regression of ROP stages were considered initial successes of the treatment. Additional treatment was performed in the absence of regression in plus disease and the occurrence of progression and neovascularization within 1 week after the LP. As an additional treatment, LP application to the ridge posterior in zone 2 was preferred, particularly in the infants with dense fibrovascular proliferative components, and rescue IVB application was preferred in infants with zone 1 ROP and with APROP. Subsequently, follow-ups were performed for every 3–4 weeks until the manifestations of ROP regressed. All infants were assessed regarding their anatomical outcomes at the corrected age of 1 year. Follow-ups after the age of 1 continued for every 4 months.

Statistical analysis

The results obtained from the study were analysed using the software of "SPSS 15.0 for Windows". The conformity of data to normal distribution was tested through the Kolmogorov-Smirnov test and the homogeneity of the variances was tested using the Levene's test of homogeneity of variance. The chi-square test was used for the analysis of categorical data. The Mann Whitney U test was used for comparisons between 2 independent groups that did not meet the parametric test assumptions, and the Kruskal-Wallis variance analysis was used for comparisons between more than 2 independent groups that did not meet the parametric test assumptions. The Mann-Whitney U test was used for binary comparisons, and statistical significance was assessed through Bonferroni correction. Test results were considered statistically significant for binary comparisons at $p < 0.017$. Continuous numerical data were described as mean ± standard deviation and categorical data as numbers (percentage). In order to assess the statistical significance, the cut-off point of the error rate (p-value) was chosen as 0.05. Test results were considered significant at $p<0.05$.

RESULTS

A total of 437 eyes (unilateral eyes in 13 cases) of 225 infants that consisted of 103 (45.8%) female and 122 (54.2%) males were included in the study. The mean BW of the infants included in the study was 1316 ± 392 g (range: 600-2850 g), and the mean GA was 29.4 ± 2.7 weeks (range: 24-36 weeks). In addition, 30 (13.3%) of the infants had a GA of 33 weeks or later.

Of the eyes that underwent LP, 109 (24.9%) were located in zone 1, while 328 (75.1%) of these were located in zone 2. The mean number of laser spots applied to the eyes throughout the first LP was 1693 ± 518 (range: 700-3500). The treatment results of the infants who were treated with LP are summarised in Table 1 regarding zones. Upon comparison of the mean number of laser spots in infants with zone 1 and zone 2 ROP, it was determined that a statistically significant higher rate of laser spots was applied to the infants with zone 1 ROP ($p < 0.001$). When additional treatment requirements were evaluated based on the zones, it was determined to be significantly lower in the

Table 1: *Treatment results of infants who underwent laser photocoagulation regarding zones.*

	Zone 1 ROP	Zone 2 ROP	*P* value
Number of eyes	109	328	
PMA during treatment (weeks), Mean±SD	36.76 ± 2.01	37.31 ± 3.41	**0.002**
Number of laser spots Mean±SD	2346 ± 506	1476 ± 280	**< 0.001**
Success of initial treatment, n (%)	93 (85.3)	304 (92.7)	**0.021**
Requirement for additional treatment n (%)	16 (14.7)	24 (7.3)	**< 0.021**
Unfavorable structural outcome, n (%)	2 (1.8)	2 (0.6)	0.245

ROP: Retinopathy of prematurity, **PMA**: Post-menstrual age, **SD**: Standard deviation
Bold font indicates statistical significance

infants with zone 2 ROP compared to the infants with zone 1 ROP (p <0.001) (Table 1).

Table 2 indicates the treatment results of the infants who were included in the study with regard to their ROP types. When additional treatment requirements were examined in terms of ROP types, it was determined that 14 eyes (58.3%) with APROP and 26 eyes (9.2%) with type 1 ROP required additional treatment, whereas there was no need for additional treatment in infants with type 2 ROP; and it was also found that the difference between the groups was statistically significant (p<0.001). Moreover, upon assessing the success of the initial therapy, it was identified that following the initial LP therapy, there was a complete regression in 258 (90.8%) eyes with type 1 ROP, in all of the eyes with type 2 ROP (100%) and in 10 (41.7%) eyes with APROP; there was also a statistically significant difference between them (p<0.001).

The mean post-menstrual age of all infants during the initial LP was 37.28 ± 2.1 weeks. When the mean post-menstrual age during LP were compared in terms of ROP types, a statistically significant difference between all groups was determined (p<0.001) (Table 2). In all of the binary comparisons, a significant difference was found between the groups (type 1 ROP and type 2 ROP, type 1 ROP and APROP, type 2 ROP and APROP) in terms of the mean time of treatment (p<0.001, p=0.011, p<0.001, respectively).

After the initial LP, manifestations of ROP regressed fully in 397 (90.8%) eyes, and additional treatment was not necessitated, whereas for 40 eyes (9.2%) additional treatment was required. Of these infants, 18 (45%) eyes underwent a rescue IVB, while an LP was applied at the posterior ridge of 16 (40%) eyes, and additional LP was applied in 6 (15%) eyes. Of these infants, dense fibrovascular membranes extending to the vitreous in zone 1 were found in 1 infant, who was born with APROP at the 28th week of gestation, and was referred to our clinic for postnatal 8th-week treatment; LP was performed. Since there was no regression in the plus disease on the 5th day in this infant, rescue IVB was applied, and upon the occurrence of retinal detachment (stage 4b), the infants were subsequently referred to an advanced health care centre.

The mean GA was 33.6 ± 0.8 (range: 33-36 weeks) weeks and the mean BW was 1881 ± 347 (range: 1480-2850 g) g in the cases who underwent LP for 33 weeks or more. Of these eyes, 16 (28.6%) were located in zone 1 and 40 (71.4%) in zone 2. Specifically, 51 eyes had type 1 ROP,

Table 2: *Treatment results of infants who underwent laser photocoagulation regarding types of ROP.*

	All of the Patients	Type 1 ROP	Type 2 ROP	APROP	*P value*
Number of eyes	437	284	129	24	
PMA during treatment LP (weeks), Mean±SD	37.28 ± 2.1	37.0 ± 3.4	38.03 ± 2.4	36.5 ± 2.3	**< 0.001**
Number of laser spots Mean±SD	1693.5 ± 518	1719 ± 462	1416 ± 265	2879 ± 414	**< 0.001**
Success of initial treatment, n (%)	401 (91.8)	258 (90.8)	129 (100)	10 (41.7)	**< 0.001**
Requirement for additional treatment, n (%)	18 (8.2)	26 (9.2)	0	14 (58.3)	**< 0.001**
Unfavorable structural outcome, n (%)	4 (0.9)	2 (0.7)	0	2 (8.3)	**< 0.001**

ROP: Retinopathy of prematurity, **PMA**: Post-menstrual age, **SD**: Standard deviation
Bold font indicates statistical significance

4 eyes had APROP, and 1 eye had type 2 ROP. In cases at born 33 weeks and more were performed LP at mean 5.6 ± 0.7 weeks after birth (range: 4–7 weeks) and the mean postmenstrual age was 39.2 ± 1.1 weeks (range: 37–42 weeks). After LP, ROP findings completely regressed in 50 (89.3%) eyes and additional treatment was not required, while additional treatment was required in 6 (10.7%) eyes. Of these cases, rescue IVB was applied in 4 (66.7%) eyes and LP was applied to the posterior ridge in 2 (33.3%) eyes. After additional treatments, ROP findings regressed in all of these cases and no unfavourable anatomic outcome was observed at the corrected age of 1 year.

Cataract or anterior segment ischaemia was not detected in any of the infants following the initial LP therapy. However, the occurrence of intravitreal haemorrhage was observed in 8 (1.8%) eyes and hyphema in 2 (0.4%) eyes. Furthermore, unfavourable anatomic outcomes were detected in 4 eyes (0.9%) of 2 infants at the corrected age of 1 year (involving retinal detachment in 2 eyes of 1 infant and dragging of the optic disc and macula in 2 eyes of 1 infant).

DISCUSSION

ROP is one of the leading causes of blindness that can be prevented generally through treatment during childhood[2]. Recently, the incidence rate of ROP has increased, particularly in developing countries, because of the development of neonatal intensive care units and the escalation in the number of surviving premature infants[14]. Given the results of the conducted research, it is considered that the ablation of the avascular retina through LP is a safe, effective and standard method in the treatment of ROP[7,15,16]. In this study, we intended to assess the efficiency of the treatment, additional treatment requirements and additional treatment results in infants who underwent LP between 2013 and 2018 in our province.

The mean GA and BW of infants who underwent LP were higher in our study compared to those in both ETROP and Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) research[6,11]. This might be due to the inclusion of infants who weighed less than 1250 g in the CRYO-ROP and ETROP study. This result might be due to the fact that 30 of the infants in our study who required treatment were at the 33rd week and older. Previous researches revealed that severe ROP develops in preterm infants with heavier BW and older GA in developing countries compared to those in the developed countries[14,17,18]. Upon reviewing the literature in our country, it was detected that the prevalence of severe ROP in late preterm infants born between the 32nd and 35th weeks of gestation was reported as 2.5% by Tiryaki Demir et al.[19], while the prevalence of severe ROP in infants older than 32 weeks was revealed as 0.6% in a prospective, multi-centred, large-scaled TR ROP study by Bas et al.[14]. Günay et al. revealed that the mean GA of the infants to whom they applied LP was 28.13 ± 1.9 weeks and the mean BW was 1147 ± 341 g; they also suggested that uncontrolled oxygen administration, a lack of ROP screenings of preterm babies, the ROP disease itself as well as its risk factors, and a lack of awareness might contribute to an increased incidence of disease and severe retinopathy in more mature premature neonates[20].

Many studies have suggested that the success rate of laser therapy is above 90%[21,22]. However, it has also been revealed that despite intensive laser therapy, the disease progresses in infants with zone 1 ROP and leads to unfavourable structural outcomes[23-25]. We found in our study that the manifestations of ROP regressed completely in 90.8% of the infants following the initial LP, and 9.2% of our infants required an additional treatment. Moreover, the additional treatment requirements of the infants with zone 1 ROP were higher compared with infants with zone 2 ROP. Likewise, the requirement for additional treatment was higher in infants with APROP.

IVB monotherapy manifested a significant benefit, in particular for zone 1 at stage 3 ROP compared to conventional LP[8]. Furthermore, many clinicians choose to conduct IVB injection combined with LP or before surgery to ameliorate post-surgical outcomes[9,10]. It has been revealed that IVB administration, particularly delayed use of it, can lead to tractional retinal detachment due to the vitreoretinal fibrous membrane, which is called the "Crunch" phenomenon, though anti-VEGF use has become increasingly widespread in posterior ROPs[26]. In our study, we performed IVB as a rescue therapy, particularly in infants with zone 1 whose ROP did not regress in the first week despite intensive LP treatment. However, after rescue IVB, we detected retinal detachment in 2 of 18 eyes (referred to our clinic at the post-gestational 7th week due to AP ROP) and unfavourable structural outcomes in long-term follow-ups. However, some studies have put forward that applying LP to the ridge posterior along with the avascular retina decreases or even hinders progression to retinal detachment[27-29]. In our study, we found that the plus disease after conventional LP was not regressed in infants with severe stage 3 ROP in zone 2 and that there were dense fibrovascular membranes extending to the vitreous; thus, we applied LP to the ridge posterior of the infant's eye. Our findings were analogous to the literature, and complete regression occurred in all our infants.

Many studies in the literature have revealed that the rates of favourable structural outcomes are higher with intensive laser therapies[16,30,31]. Rezai et al. applied a mean of 2534 confluent laser spots in zone 1 ROP and a mean of 1850 in zone 2 ROP to 44 eyes with threshold ROP and achieved favourable anatomical success in 93% of the infants. Banach et al.[16] revealed remarkable treatment success through applying confluent laser burns to the avascular retina. They reported that merely 3.6% of intensively treated eyes progressed, compared to 29.4% of eyes with a less intensive treatment modality. Gonzales et al.[31] reported a lower rate of progression to retinal detachment in their cohorts of infants treated with confluent LPC. Likewise, we applied near confluent laser treatment in our study to all infants with zone 1 and zone 2 ROP, and we achieved a treatment success in 90.8% of the infants after the initial treatment. Moreover, the results of these studies verify our findings in terms of proper anatomical outcomes.

Current treatment guidelines based on randomized controlled ETROP trial results recommend treatment for type 1 ROP and close follow-up for type 2 ROP (11). However, in real-life ROP applications, decision-making is complex. Because delay in ROP treatment can cause permanent vision loss, sometimes ROP specialists tend to treat this dynamic disease at an earlier stage, as a result of various medicolegal (fear of litigation due to increased liability claims for ROP care providers and increasing number of desicions against interested ophthalmologists) and logistical causes (the need for repeated long-distance travel and insufficient adaptation of parents for close follow-ups)[32-39]. In a questionnaire-based study of ophthalmologists participating in ROP treatment in the United Kingdom, 27% of 654 treated eyes were diagnosed with ROP less than type 1 ROP[33]. In a study of 1444 eyes of 722 infants from 6 institutions in the United States, Gupta and et al.[34] found that 13 (9.5%) of 137 eyes treated for ROP were treated with a clinical diagnosis less severe than type 1 ROP. In India, Renu P. Rajan et al.[35] reported that 33 eyes (13.7%) of 241 eyes treated between 2016 and 2019 were treated outside the guidelines. The reported indications for treatment in these studies included persistent ROP despite advanced postmenstrual age (>41 weeks), structural changes related to future anatomical complications (such as vitreoretinal traction and macular ectopia), persistent stage 3 ROP for >6 weeks, preretinal and/or intravitreal hemorrhage, other eye type 1 ROP presence and logistic concerns[32-35]. In our current study, 129 eyes were treated earlier than type 1 ROP due to the worriying structural findings related to anatomic complications that may occur in the future and logistical problems in the 6-year period between 2013-2019, and no unfavourable structural outcomes were observed in any of these eyes.

In the study, unfavourable anatomic outcomes were observed among 4 (0.9%) eyes in our research, following the initial LP treatment and the additional treatments that were applied subsequently. It has been put forward in the literature that severe prematurity and more severe forms of the disease are substantially associated with unfavourable anatomic outcomes[40-42]. In our study, an unfavourable anatomic outcome was determined in 8.3% of eyes with APROP and in 0.7% of infants with type 1 ROP, and the difference between them was found to be statistically significant.

The limitation of this study is that it is retrospective, and long-term impacts of LP treatment, such as strabismus and myopia, in the infants who were included in the study were not investigated.

In the present study, infants with zone 1 ROP were treated significantly earlier compared to infants with zone 2 ROP, and infants with APROP were treated earlier than the infants with type 1 and type 2 ROP. As well, thanks to the close follow-ups after the initial LP treatment and additional treatments, which were applied on time, anatomical success was achieved in 99.1% of the infants. Consequently, the timely near confluent LP that is combined with accurate and timely screening examinations is considered an effective treatment, particularly for type 1 and type 2 ROPs. Nevertheless, it was detected in infants with APROP that the manifestations did not regress with initial LP in almost half of the infants, and additional treatments were needed. Furthermore, LP application to the posterior of the ridge in infants with zone 2 ROP and rescue IVB treatment applied in infants with zone 1 ROP and APROP in the early period (without the formation of dense fibrovascular proliferative membranes) was determined to increase the favourable structural outcomes, though the number of infants was low.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Funding: The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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