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Retinopathy of Prematurity Treatment Trends from 2003-2020 in the United States

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Abstract

We used population-based data obtained from Optum's Clinformatics® Data Mart Database to characterize recent trends in retinopathy of prematurity (ROP) treatments and outcomes in the United States. Laser photocoagulation was utilized more frequently every year compared to anti-VEGF.

Retinopathy of prematurity (ROP) is a leading cause of blindness in children in the United States, despite treatment.[1–3] Laser and anti-vascular endothelial growth factor injections (anti-VEGF) are the primary treatment for ROP.[4–7] We evaluated utilization of laser and anti-VEGF and associated adverse outcomes from 2003 to 2020.

Data from Optum's Clinformatics® Data Mart Database, a de-identified database containing commercial and Medicare Advantage from all 50 states was provided by Stanford Center for Population Health Sciences (PHS) Data Core. This study was approved by the Stanford Institutional Review Board and the study adhered to the Declaration of Helsinki. Claims between January 1, 2003 to June 30, 2020 were linked to associated *International Classification of Diseases, Ninth Revision (ICD-9)* and *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10)* diagnostic codes and *Current Procedural Terminology* (*CPT*) billing codes. We included all infants born since January 1, 2003 with an associated ICD-9 or ICD-10 code related to a diagnosis of prematurity (Supplemental Table 1, **available at** www.aaojournal.org) and studied all infants with a birth weight <1500g or gestational age <30 weeks. ROP status was determined using ICD codes. Primary interventions were assessed by the following CPT codes: Laser (67105,

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Conflict of Interest: No conflicting relationship exists for any author.

The manuscript has not been previously published and is not under consideration in the same or substantially similar form in another journal. A portion of this investigation was presented at the 2019 American Medical Association Research Symposium as a poster. This study was also accepted for an oral presentation at the 2020 American Association for Pediatric Ophthalmology and Strabismus Annual Meeting but was not presented due to COVID-19.

67145, 67210, 67220, 67228, 67229), anti-VEGF therapy (67028), and incisional retinal detachment repair (67036, 67039-67043, 67107, 67113, 67105, 67101).

Data analyses were performed using R (R Core Team, 2021). Population characteristics were summarized as means/standard deviations or as percentages analyzed by χ^2 testing. Given small sample sizes for subgroups, Fisher's Exact test was utilized to assess differences in the likelihood of receiving laser, anti-VEGF, or combination therapy. Per institutional PHS guidelines, all subgroups with a cell size <15 were labelled as such or masked to prevent re-identification. Counts for ROP treatments and Stage 4-5 outcomes were plotted by year from 2003-2020 using first recorded dates. Binomial logistic regression modeling was performed to analyze associations between birth weight, gestational age, gender, year of management and ROP treatment modality. A two-sided P <0.05 was considered statistically significant.

Between 2003-2020 there were 19,997,630,418 insurance claims (66,853,547 patients) used to identify 184,750 premature infants and 31,606 infants at increased risk for ROP (Supplemental Figure 1, **available at** www.aaojournal.org). In high-risk infants, 8,384 had an ROP diagnosis and 489 (5.8%) received treatment with laser, anti-VEGF, or both. There was a male preponderance (51.6%). ROP incidence was 4.5% for premature and 26.5% for high-risk infants (incidence rates of 2.6 and 15.2 ROP cases/1000 premature infants/year, respectively). Laser was the most common treatment (Figure 1, supplemental Figure 1). Anti-VEGF monotherapy increased between 2009-2011 and 2015-2017. The majority (72.4%) of combination patients received anti-VEGF prior to laser.

Characteristics of ROP patients by treatment modality are shown in (Supplemental Table 2, **available at** www.aaojournal.org). For ROP patients, laser (80.7%) was more common than either anti-VEGF monotherapy (13.3%) or combination therapy (5.9%). Male and female infants were treated with laser at similar rates (49.2% vs 50.8%). Females were less likely to receive anti-VEGF vs laser monotherapy: OR 57 (95% CI:0.33-0.98), p=0.045.

Extremely low birth weight (<1000g) was not correlated with anti-VEGF usage compared to laser: OR 1.08 (95% CI:0.43-2.71), p=0.86. Binomial logistic modelling with stepwise adjustment for birth weight, gender, and year of treatment revealed that year of management closer to 2017 independently was associated with increased anti-VEGF usage, with female infants independently less likely to receive anti-VEGF treatment: OR 0.52, (95% CI:0.27-0.99), p=0.048.

Stage 4-5 ROP was diagnosed in 61 (0.72%) infants: 34 infants had previous laser, anti-VEGF, or combination therapy. There was no difference between laser and anti-VEGF for Stage 4-5 ROP (7.1% vs 3.1%, Fisher exact p=0.29). In Stage 4 ROP (n=43) patients, 15 went on to receive some form of retinal detachment intervention. In Stage 5 (n= 18), nearly half had not received any previous ROP treatment or subsequent retinal detachment intervention (exact percentages masked as n<15).

Herein we characterize trends in the usage and associated outcomes of laser and anti-VEGF intravitreal injections for ROP in the United States. Laser continued to be utilized more frequently throughout the study period, with anti-VEGF gaining recently. This tread has been documented by other studies as well.[2,3] We report incidence rates of 2.6 and 15.2 ROP cases per 1000 infants per year, for premature and high-risk premature, respectively. Overall, 4.5% of premature infants and 26.5% of high-risk premature infants developed ROP, with 5.7% of ROP patients receiving treatment.

Female infants appeared to be less likely to receive anti-VEGF compared to laser monotherapy even with adjustments made for extremely low birth weight/gestational age and year of intervention: OR 0.57 (95% CI:0.33-0.98), p=0.045. In extremely low birth weight infants (<1000g) and extremely early gestational age infants (≤26 weeks) there were no identifiable treatment preference; we were unable to account for Zone and Plus. The rate of Stage 4-5 ROP retinal detachments was approximately 1/140 for infants diagnosed with ROP. We found that neither laser nor anti-VEGF were more likely to result in Stage 4-5 ROP detachments. Granular data on zone, Plus, and stage was lacking.

Limitations of this study revolve around a lack of data because of ICD-9 and ICD-10 coding and generalizability beyond privately insured children in the Clinformatics® dataset. Our database did not include information on zone of ROP, Plus, geographic location, number of years providers has been practicing, or preexisting neurologic comorbidities, which may all be associated with ROP treatment modality or outcomes. Given that our dataset only includes commercial and Medicare Advantage health insurance claims, it may not be representative of the US population at large. Potential claims coding errors by physicians may also exist within our database, though these errors would represent non-differential classification of the exposure and bias our results towards the null.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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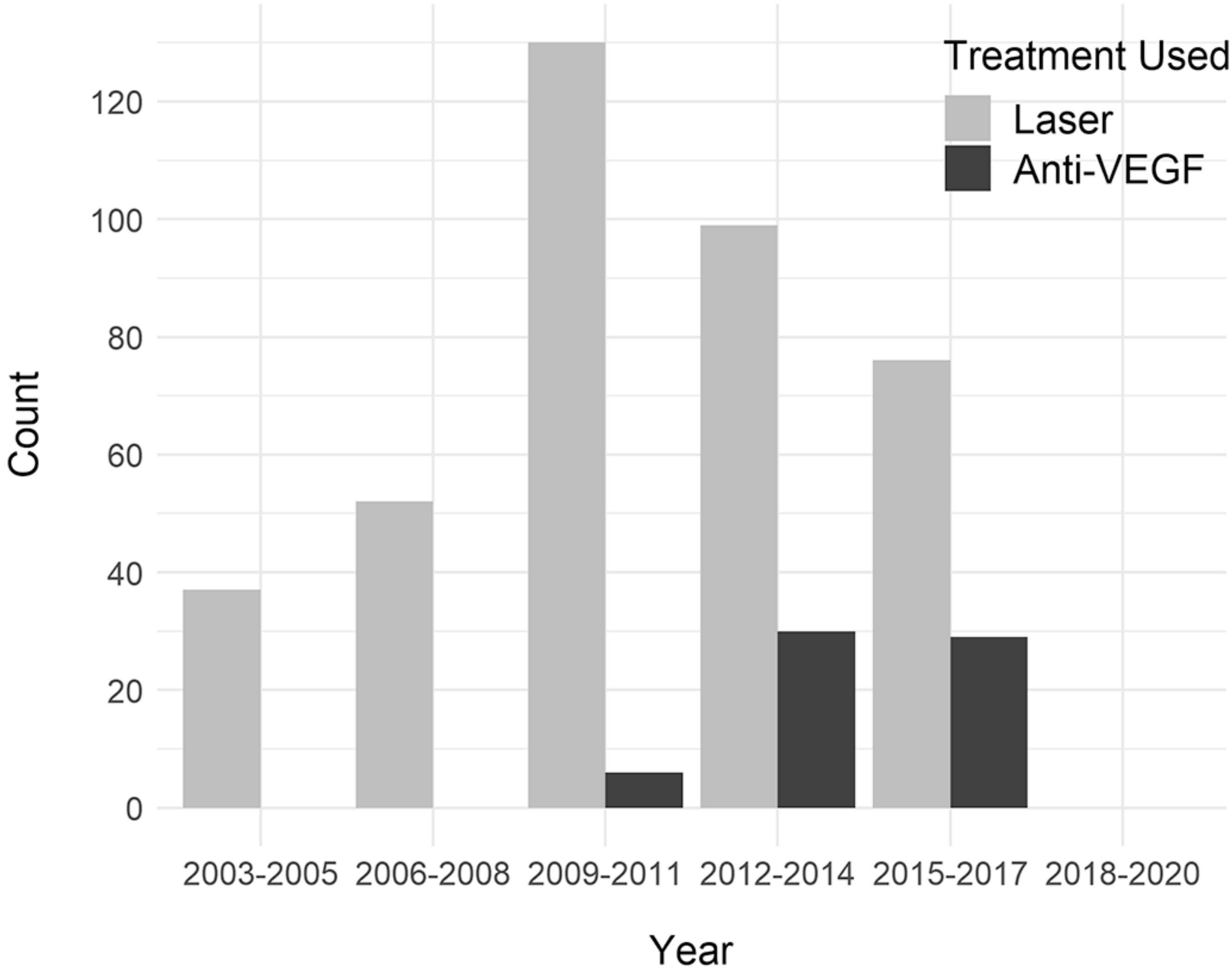

Figure 1:
Usage of laser photocoagulation and Anti-VEGF treatments between 2003-2020 in the Optum Clinformatics® Data Mart Database. Laser therapy continues to be most frequently used, but Anti-VEGF usage had an uptick beginning in 2011. Although 43 patients were diagnosed with ROP in our dataset between January 1, 2018-June 30, 2020, none were treated with solo- laser or Anti-VEGF. The exact counts for Anti-VEGF in 2009-2011 and the combination therapy group are masked due to N <15.