

Intraocular Pressure and Central Corneal Thickness in Premature Newborns: A Systematic Review with Meta-Analysis

Prematüre Yenidoğanlarda Göz İçi Basıncı ve Merkezi Kornea Kalınlığı: Sistematik Bir İnceleme ve Metaanaliz

^{id} Kalina TRIFONOVA^a, ^{id} Kiril SLAVEYKOV^b, ^{id} Hristo MUMDZHIEV^c

^aDepartment of Ophthalmology and Otorhinolaryngology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

^bFirst Department of Internal Diseases and General Medicine, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

^cDepartment of Neonatology, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

ABSTRACT Objective: Our study aimed to summarize and analyze the available information in the up-to-date literature, concerning intraocular pressure and central corneal thickness values in premature newborns. **Material and Methods:** We conducted a comprehensive literature review, gathering information from PubMed, Scopus, Embase, Google Scholar, and free-text searches on the topic. We chose only 14 of them to perform a meta-analysis. We used Review Manager 5.4 to compare the mean values of intraocular pressure and central corneal thickness between full-term and premature newborns. **Results:** The results of the mean value of intraocular pressure of premature infants varied significantly according to different authors-from 10 mmHg to 29 mmHg. Most of the research showed higher intraocular pressure and thicker corneas in premature infants compared to full-term ones. Many researchers looked for a positive correlation between the increased central corneal thickness in premature newborns and the increased intraocular pressure but showed conflicting results. Our meta-analysis showed that the intraocular pressure and central corneal thickness in premature newborns were significantly higher compared to full-term infants with mean difference of 1.95 mmHg [Confidence interval (CI) 0.62-3.28] and 57.82 μ m (CI 34.46-81.18), respectively. **Conclusion:** Additional studies tracking changes in both intraocular pressure and central corneal thickness values, with larger sample sizes and in a longitudinal design with better-differentiated sample groups, are warranted.

Keywords: Preterm; infants; central corneal thickness; intraocular pressure

ÖZET Amaç: Çalışmamız, prematüre yenidoğanlarda göz içi basıncı ve merkezi kornea kalınlığı değerleri hakkında güncel literatürde mevcut bilgileri özetlemeyi ve analiz etmeyi amaçlamaktadır. **Gereç ve Yöntemler:** PubMed, Scopus, Embase, Google Akademik ve konuyla ilgili ücretsiz metin aramalarından bilgiler toplayarak kapsamlı bir literatür incelemesi yürüttük. Yalnızca 14 tanesini metaanaliz yapmak için seçtik. Tam süreli ve prematüre yenidoğanlar arasında göz içi basıncı ve merkezi kornea kalınlığı ortalama değerlerini karşılaştırmak için Review Manager 5.4 programını kullandık. **Bulgular:** Prematüre bebeklerin göz içi basıncının ortalama değerinin sonuçları, farklı yazarlara göre 10 mmHg ile 29 mmHg arasında önemli ölçüde değişmiştir. Araştırmaların çoğu, prematüre bebeklerde tam zamanında doğanlara kıyasla daha yüksek göz içi basıncı ve daha kalın korneaların olduğunu göstermiştir. Birçok araştırmacı, prematüre yenidoğanlarda artmış merkezi kornea kalınlığı ile artmış göz içi basıncı arasında pozitif bir korelasyon aramış, ancak çelişkili sonuçlar elde etmiştir. Metaanalizimiz, prematüre yenidoğanlarda göz içi basıncının ve merkezi kornea kalınlığının, sırasıyla ortalama 1,95 mmHg [Güven aralığı (GA) 0,62-3,28] ve 57,82 μ m (GA 34,46-81,18) fark ile tam zamanında doğan bebeklere göre anlamlı olarak daha yüksek olduğunu göstermiştir. **Sonuç:** Hem göz içi basıncı hem de merkezi kornea kalınlığı değerlerindeki değişimleri izleyen, daha büyük örneklem boyutlarına ve daha iyi ayrıştırılmış örneklem gruplarıyla uzun süreli bir tasarımda ek çalışmalar yapılması gerekmektedir.

Anahtar Kelimeler: Prematüre; bebekler; merkezi kornea kalınlığı; göz içi basıncı

Premature infants have serious health issues from the day they are born. It is important to know their anatomical and physiological differences from

full-term newborns so that we do not misdiagnose, overtreat or underestimate an existing problem. The visual system can suffer serious consequences from

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Correspondence: Kiril SLAVEYKOV

First Department of Internal Diseases and General Medicine, Medical Faculty, Trakia University, Stara Zagora, Bulgaria

E-mail: kirilslaveykov@gmail.com



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prematurity, as most widely discussed matter in the literature is the threat of developing retinopathy of prematurity. However, other problems often occur like strabismus, refractive errors, particularly myopia and cerebral vision impairment.¹ Thiagarajah et al. found in a retrospective study which included 247 premature infants that 2% had congenital glaucoma which is significantly higher than the general population.² The authors think that the premature birth led to termination of the development of the trabecular meshwork or angle. Other authors did not find a connection between primary congenital glaucoma and prematurity.³ However, those two conditions can co-exist and are both potentially blinding and need to be diagnosed and treated on time. Ricci speculated that even the slightly increased intraocular pressure (IOP) in premature newborns could facilitate the development of retinopathy of prematurity because it can lead to a significant reduction in the ocular perfusion pressure.⁴ Central corneal thickness (CCT) has been associated with glaucoma risk in adults but the normal values for full-term infants may not be relevant to infants who are born prematurely.⁵ A thick cornea may result in an overestimation of the actual IOP measured by the Goldmann Applanation Tonometer. Everything mentioned so far emphasizes the importance of knowing the normal ranges of IOP and CCT in premature infants. Our study aimed to summarize and analyze the available information in the up-to-date literature.

MATERIAL AND METHODS

We conducted a comprehensive literature review, gathering information from PubMed (US National Library of Medicine); Scopus (Elsevier, Netherlands); Embase (Elsevier, Netherlands); Google scholar (Google; US), and free-text searches on the topic. We used the following key words in our search-“intraocular pressure”, “central corneal thickness”, “preterm”, “premature”, “infants”, “newborns”, “neonates” and “babies”. We used Prisma Checklist and created a Prisma Flowchart showing our comprehensive search and inclusion and exclusion criteria (Figure 1). The study selection and data extraction were performed by all three authors. We identified 1,862 records through database search and

we removed 617 of them due to duplication and unobtainability. After removing the unrelated articles; editorials/letters/notes; studies not performed in humans; including only one of the key words; only titles; studies related to factors other than weight and postconceptional age (PCA) affecting CCT and IOP; studies that compared the IOP of preterm and full-term infants and adults and studies of CCT and IOP in children only 192 articles were left for analysis. After removing the articles which were not in English; articles researching CCT and IOP only in full-term babies and other unrelated and not obtainable articles only 40 were left fit for analysis. From them, we chose only those articles that researched the IOP and CCT in premature and full-term newborns and only 14 articles were included in the final meta-analysis. We created two forest plots with a random effect model by using Review Manager 5.4 and we measured the mean differences of IOP and CCT between premature and full-term newborns.

The authors declare that the study was carried out in accordance with the Helsinki Declaration principles.

The research was approved by the ethics committee of Trakia University-Stara Zagora, Protocol 19/ 2021 on the 16th of May.

RESULTS

Many teams have tried to estimate the mean IOP in premature newborns throughout the years. However, there has been a great variation between the results in different studies. In the first group of studies, the authors tried to estimate the IOP in premature infants in a cross-sectional design (Table 1).⁶⁻¹¹ In all of them the IOP was measured only once within the first week after birth and/or when the newborns were sufficiently stable. Their results of the mean value of IOP varied significantly, from 10 mmHg to 29 mmHg. The greatest limitations of these studies were the small sample size (range from 21-70 patients) and the heterogenous groups of patients. Since the outcome and exposure variables are measured at the same time, it is relatively difficult to establish causal relationships from a cross-sectional study. Even though some of the studies were done with the same type of

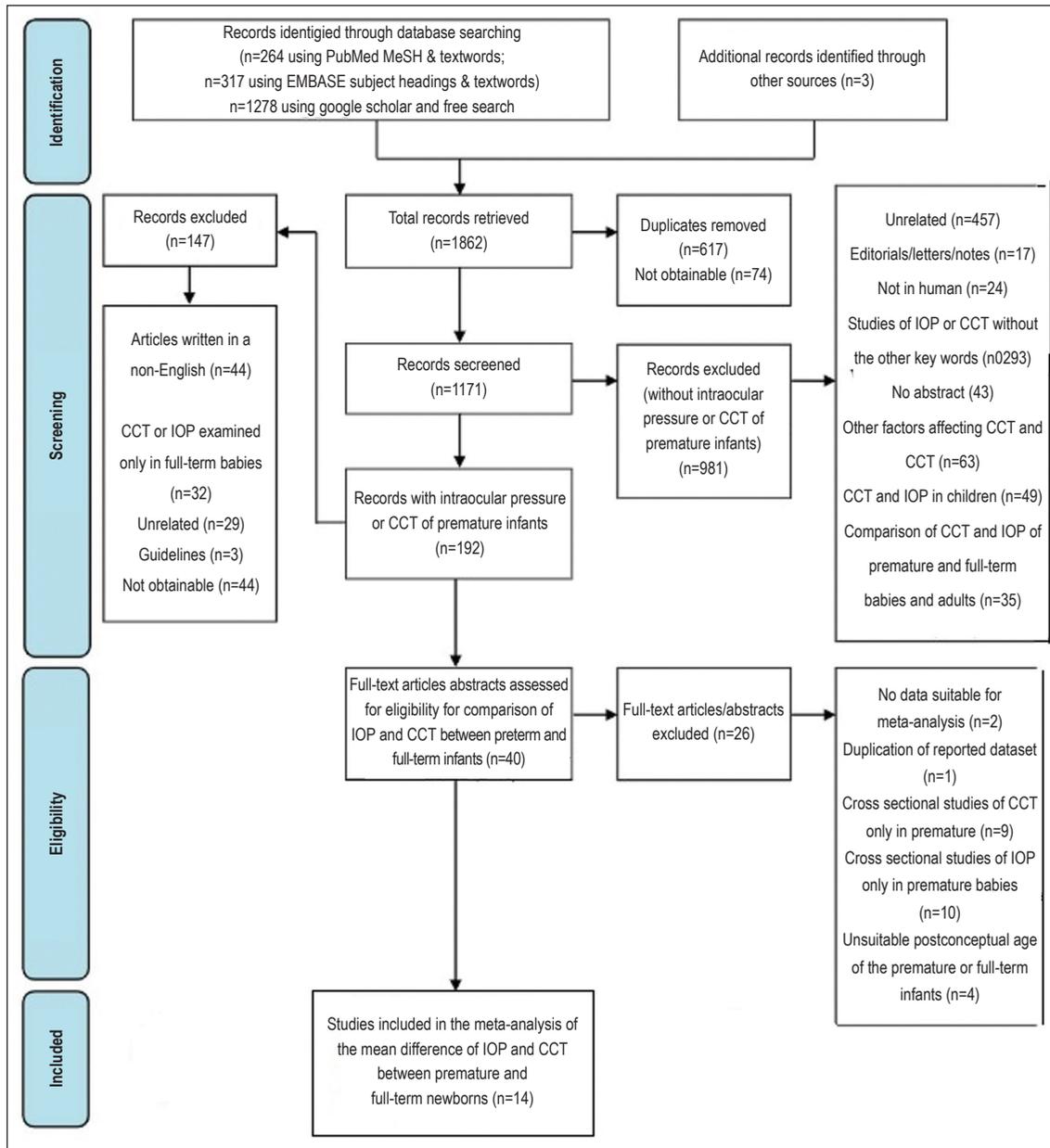


FIGURE 1: Prisma flow diagram for the systematic review of CCT and IOP in premature newborns. IOP: Intraocular pressure; CCT: Central corneal thickness.

tonometer (Tono-pen), their results still showed a significant variation (from 10.3 mmHg to 24 mmHg).^{6-8,10} Haus et al. were the first to compare the mean IOP measured with ICare rebound tonometer (Revenio group Corporation, USA) and Tono-pen XL tonometer in premature newborns.⁷ They found a significant difference between the results achieved with those two devices. IOP values were significantly lower when evaluated by ICare rebound tonometer rather than by the Tono-pen. According to these authors

ICare rebound tonometer reflected better the IOP and Tono-pen measurements were falsely elevated due to defense and discomfort reactions to the anesthetic eye drops and the larger size of the eyelid opening. Both the teams of Tucker et al. and Spierer et al. did not find correlation with the gestational age and birth weight of the infants.⁶ On the contrary, two more recent studies by Khaja et al. and Grover et al. showed a correlation between the IOP and the gestational age and birth weight of the newborns.^{10,11} Four other

TABLE 1: Cross-sectional studies of IOP of premature infants.

	Author/year	Type of tonometer	Subjects (n*)	GA* (weeks)	Mean IOP* (mmHg)
1.	Tucker ⁶ , Canada, 1992	Tonopen II	70	<37	10.3
2.	Haus ⁷ , Germany, 2008	Tono-Pen XL ICare	69	28.4	16 9
3.	Jeon ⁸ , Korea, 2009	Tono-pen	58	<37	15.14±4.64 of right eye 15.29±3.70 of left eye
4.	Zengin ⁹ , Türkiye, 2014	--	---	---	17.2
5.	Khaja ¹⁰ , USA, 2014	Tono-pen XL	24	34.3	24.28
6.	Grover ¹¹ , USA, 2016	---	45	28.2+/-2.3	29.0±9.0

*n-number of patients; IOP: Intraocular pressure; GA: Gestational age.

teams also did cross-sectional studies but compared the IOP between premature and full-term babies.¹²⁻¹⁵ They all showed significantly higher IOP in premature compared to full-term newborns. Only the study of Muslubas et al. did not find significant difference probably due to the higher postconceptual age of the premature infants (36 weeks).¹³ Other research teams did longitudinal studies of IOP in premature newborns to follow its changes with their maturation.^{2,16-21} All of the studies showed a statistically significant ($p<0.01$) decline of IOP values with a negative correlation between the postconceptual age and birth weight of the infants. Only Choo et al. did not find a statistically significant difference in IOP between premature and full-term newborns.²²

Since the relationship between CCT and IOP is a well-known entity, many researchers looked for a correlation between the increased CCT in premature newborn babies and the increased IOP compared to full-term newborns. The team of Khaja found that premature newborns, without any obvious eye disease, showed increased IOP values and increased CCT as compared to adults.¹⁰ There was a positive, but weak correlation between IOP and CCT in preterm infants. The team of Grover also found higher IOP and thicker CCT in premature infants compared to adults but no correlation between the two.¹¹ The teams of Uva et al. and Acar et al. showed that there was a correlation between CCT and IOP, which both declined with the maturation of the infant.^{12,15} However, the teams of Muslubas et al. and Karahan et al. found no such correlation.^{13,14} All the mentioned studies had their limitations due to the

small sample size, heterogenous groups of the infants and cross-sectional fashion. Sekeroglu et al. were the first team to do a longitudinal study and track both values of IOP and CCT at different postconceptual ages in the same infant.¹⁸ Their results showed a positive correlation between CCT and IOP. Acar and colleagues later became the other team to show similar results.¹⁹ On the contrary Choo et al. did not find correlation between CCT and IOP. They only found negative correlation between CCT and postconceptual age of the infant.²²

Other researchers have examined only the CCT in premature infants without measuring the IOP. The CCT measurement plays an important role, especially in diagnosis and treatment of congenital glaucoma patients. Hence appropriate assessment of the CCT is mandatory in preterm infants. The study of Ehlers et al. at showed that the corneal thickness of premature and full-term babies was higher compared to adults.²³ The values were found to decrease gradually and reach the thickness in adults at the age of about 3 years. Gunay et al. found correlation between CCT and gestational age and birth weight in premature newborns.²⁴ The mentioned authors did their research in a cross-sectional manner.^{23,24} Other teams did longitudinal studies following the changes of the values of CCT with maturation of the premature newborn.²⁵⁻²⁹ They all found a negative correlation with gestational age and weight. The importance of CCT fast variations after premature birth concerns both the knowledge of anterior segment development and the correct evaluation of IOP in immature eyes.

In order to achieve increased statistical power through increased sample size and resolve the uncertainties we decided to perform a meta-analysis of all the research that we could find that measured IOP and CCT in premature and in full-term infants. We used Rev Man 5.4 to compare the mean differences between the mean values of both IOP and CCT. We couldn't use some of the research to perform meta-analysis due to insufficient data available online. We included only research in which we could find available information on IOP and/or CCT measurement of prematurely born infants performed at postconceptual age between 28-36 weeks, preferably 32 weeks. This was our attempt to avoid heterogeneity of the used samples. We excluded the research of Muslubas et al. because the premature infants in their research had an average PCA of 36 weeks which is almost full-term.¹³ We chose infants around 40 weeks PCA for the full-term research included in our meta-analysis. Ricci examined newborn babies up to one month after birth and most of them were not full-term yet.⁴ We arranged all the data by date in a table for better visualization of the information (Table 2). We included 14 articles in our meta-analysis and created two forest plots—one for each variable (Figure 2, Figure 3). In the first we analyzed IOP and included 9 of the articles, in the second we analyzed CCT and included 11 articles. We used a random effect model due to the small size of the included studies.

The pooled results showed that the mean difference of IOP between premature and full-term newborns was 1.95 mmHg [Confidence interval (CI) 0.62-3.28] favoring the preterm newborns (Figure 1). The test for overall effect showed statistical significance ($p < 0.004$). The pooled results also showed that the mean difference of CCT between premature and full-term infants was 57.82 μm (CI 34.46-81.18), strongly favoring (test for overall effect: $p < 0.000001$) the premature infants (Figure 3). Despite our attempt to choose similar studies, the I in both studies showed very high heterogeneity which was statistically significant.²

DISCUSSION

As far as we know our systematic review with meta-analysis is the first of its kind. The limitations of the

study are that few authors research this topic, and the even fewer of these are suitable for meta-analysis. The collection of data from many of the studies had high selection bias and recall bias. The meta-analysis results had some publication bias due to the closed access of some of the articles, and the inclusion only of articles in English. The results of the meta-analysis showed very high heterogeneity which means that the studies seriously vary from one another.

The great variation of IOP measurements could be partially explained with the use of different devices. Measuring the IOP in pediatric patients with Goldman tonometry is the golden standard in Ophthalmology, but since it is not possible to perform on newborns, other methods have been introduced. Studies have shown that Tono-pen and ICare are suitable devices in measuring the IOP in newborns because they are better in measuring the IOP in edematous corneas.³⁰ Gandhi et al. showed slightly higher measurement of IOP with Tono-pen XL than with Goldman applanation tonometer.³¹ However, Iester et al. did not find significant difference between the two devices and showed enough precision for accurate screening.³² ICare rebound tonometer does not require topical anesthetic and is well tolerated by children. ICare, however, in a study performed by McKee et al. showed results 2 mmHg lower than with Tono-pen and this difference was greater in corneas with edema.³³ The study by Haus et al. also showed significantly lower measurement of IOP in premature newborns with ICare compared to Tono-pen.¹³ Since CCT is significantly thicker in premature compared to full-term newborns, Tono-pen might still be the better device to measure the IOP in this age group. Shiotz tonometry is rarely used in modern ophthalmic practice because it is less accurate in children due to decreased scleral rigidity. It is no longer considered acceptable method for measuring IOP in children except if there are no other available devices.³⁴

Another explanation for measurements' variations could be the artificial increase of IOP due to increased venous pressure caused by the Valsalva maneuver produced by resisting examination, forced eyelid closure or the use of an eyelid speculum. Epley et al. showed that using an eyelid speculum elevates the IOP measurement in children by an average of 4

TABLE 2: Comparison of IOP and CCT between pre-term and full-term newborns.

Authors/type of study	Device	Premature (n*)/measurement age (weeks)	IOP* (mm Hg)	CCT* (µm)	Full term (n)	IOP (mm Hg)	CCT (µm)
1. Kirwan ²⁵ , Ireland, 2005/Longitudinal	US* pachymeter DGH 55	n=35 PCA=28.3	---	691±87	35	---	564±35
2. Ng ¹⁶ , China, 2008/Longitudinal	Tono-pen	n=104 PCA=29.8±1.1	16.57±2.4	---	104	14.6±2.4	---
3. Uva ¹² , Italy, 2011/Case-control	Tono-pen XL; Pachmate DGH-55	n=33 PCA=34±3	18.9±3.7	599±36	33	17±2.6	576±26
4. Lindenmeyer ¹⁷ , Brazil, 2012/Longitudinal	Tono-pen XL	n=50 PCA=29.7±1.6	14.9±4.5	---	50	13.1±5.9	---
5. Karahani ¹⁴ , Türkiye, 2015/Case control	Tono-pen XLTM; AccupachVI	n=63 PCA=32.7±1.7	17.5±2.1	576.5±16.4	55	16.3±1.9	562.7±18.4
6. Acar ¹⁵ , Türkiye, 2015/Case control study	Tono-Pen XL Compact Touch US system	n=89 PCA=32	19.39±2.22	653.99±42.02	49	16.86±2.93	590.67±58.26
7. Sekeroglu ¹⁸ , Türkiye, 2015/Longitudinal	Tono-Pen AVIA	n=170 PCA=35.9±2.5	14.1±1.9	568.1±22.1	170	13.7±1.7	561.6±21.4
8. Jethani ²² , 2015, India, Case control	Palm Scan AP 2000 300 AP+Paccscan Plus	n=42 PCA<37	---	620.7±88.8	43	---	574.4±78.3
9. Acar ¹⁵ , Türkiye, 2016/Longitudinal	Tono-Pen; Compact Touch US system	n=110 PCA=32	18.28±2.78	670.56±55.72	110	13.21±1.94	546.18±38.70
10. Choo ²⁷ , 2018, Malaysia/Longitudinal	ICare; Paccscan 300P USP	n=63 PCA=32.36	12.87±3.11	618.8±72.9	63	14.15±3.33	563.9±50.7
11. Balci ²⁸ , Türkiye, 2018/Longitudinal	Tono-pen	n=40 PCA=30	16.9±0.9	---	40	13.1±1.3	---
12. Sehrawat ²⁷ , India, 2019/Case-control	US Pachymeter Pachette 3	n=100 PCA=31.7±2.3	---	633.5±2.8	100	---	555.1±2.7
13. Liu ²⁹ , 2020, China/Longitudinal	PachPen	n=1726 PCA=34	---	602.67±57.26	1726	---	563.499±51.63
14. Ceilik ²⁹ , 2022, Türkiye/Longitudinal	AccuPach 6 Pachymeter	n=32 PCA=32	---	616±66.7	32	---	546.76±49.4

*n=number of patients; US: Ultrasound; PCA: Postconceptional age; CCT: Central corneal thickness; IOP: Intraocular pressure.

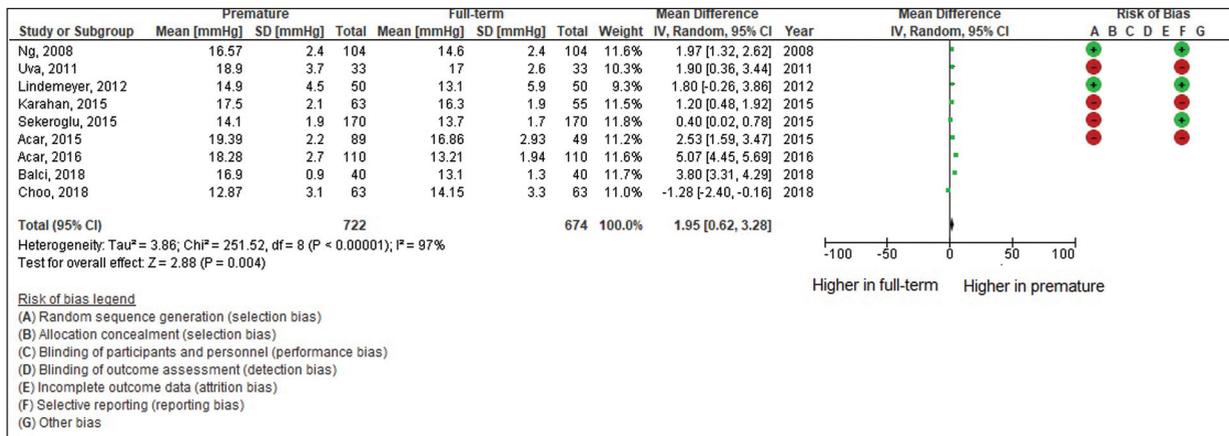


FIGURE 2: Meta-analysis of the difference of IOP between premature and full-term infants.

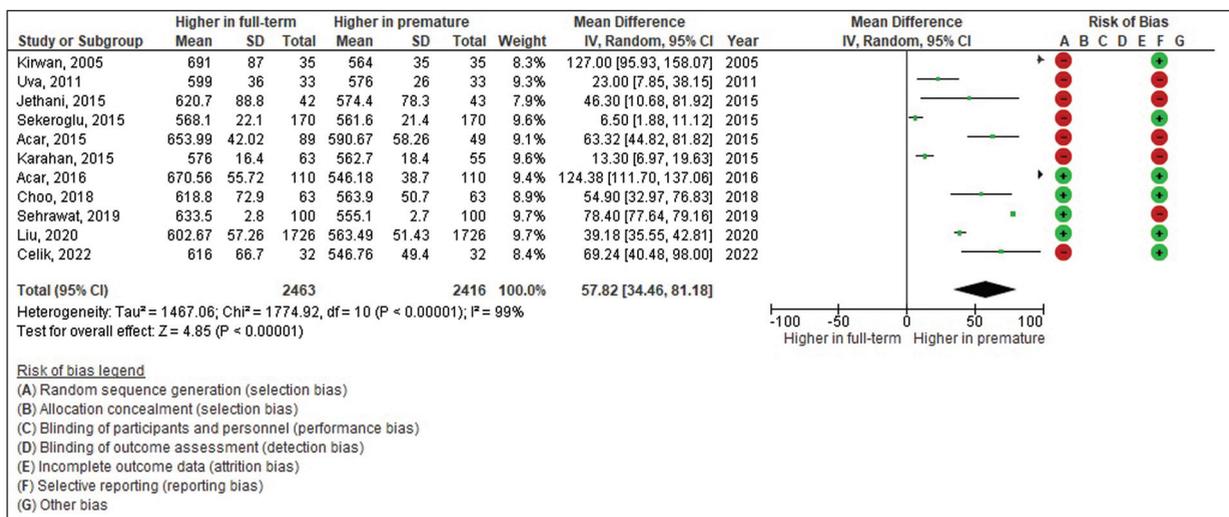


FIGURE 3: Meta-analysis of the difference of CCT between premature and full-term infants.

mm Hg.³⁵ This could be avoided by using general anesthesia. However, general anesthesia also affects the IOP, leading to its decrease. Midazolam (Fagron, Germany) is the sedation of choice according to Mikhail and team because it does not affect the IOP.³⁴ Three to five minutes need to pass after intubation in order to take an IOP measurement. The use of Icare rebound tonometer without eyelid speculum could also avoid the artificial increase of the IOP.³⁵

Many studies have shown a positive correlation between CCT and IOP.^{10,12,14,18,19} The gradual decrease of CCT after birth is due to better control of corneal hydration, corneal remodelling and stretching of collagen fibers.²⁵ However, there are also other

possible explanations for the increased IOP in premature newborns. According to Ricci, it might be a result of the maturation of the aqueous drainage system induced by the transition from the intrauterine to extrauterine environment.⁴ Karahan et al. discussed whether this phenomenon represented a programmed maturation process, related to an increase in dimensions of ocular structures under the influence of complex neuroendocrine control.¹⁴

CONCLUSION

The meta-analysis showed that the mean IOP of premature newborns was 1.95 mmHg higher and the CCT was 57.82 micrometers thicker than the IOP and CCT of

full-term infants. Even though the exact causes of the IOP decrease with maturation of the newborn are not completely clear up to this point, most of the studies showed a positive correlation with changes of CCT. Additional studies tracking changes in both IOP and CCT values, with larger sample sizes and in a longitudinal design with better-differentiated sample groups, are warranted. Other factors like mode of delivery, Apgar score, blood pressure and medications need to be included in the further analysis as well.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **Design:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **Control/Supervision:** Kalina Trifonova, Hristo Mumdzhev; **Data Collection and/or Processing:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **Analysis and/or Interpretation:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **Literature Review:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **Writing the Article:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **Critical Review:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov; **References and Findings:** Kalina Trifonova, Hristo Mumdzhev; **Materials:** Kalina Trifonova, Hristo Mumdzhev, Kiril Slaveykov.

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