ARTYKUŁ ORYGINALNY ORIGINAL RESEARCH STUDY
DOI: 10.24292/01.OT.030726
Article ID: A0008

Effect of optical correction on the stereopsis of patients with refractive accommodative esotropia and factors affecting it

Rabia Jabeen, Maryam Firdous, Farah Naheed, Saif Ullah, Rimsha Tanveer Kiyani, Sadaf Qayyum

Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan
Head: prof. dr. Ume Sughra

HIGHLIGHTS

We sought to find out if stereopsis improved with the use of glasses in refractive accommodative esotropia patients. As the amount of esotropia reduces in this group, we wanted to know if the improvement in stereopsis was also relieved by straightening (or relatively less deviation) of eyes, or if it stayed the same.

ABSTRACT

Objectives: To evaluate the effect of glasses on stereo acuity in patients presenting with refractive accommodative esotropia.
Methods: A cross-sectional study was conducted in the orthoptics department of a tertiary eye care hospital from October 2021 to January 2022. 45 patients diagnosed with refractive accommodative esotropia were included. Visual acuity, angle of deviation, and stereo acuity using the Titmus Fly test were measured. Data were analyzed using (statistical package for the social sciences) version 26.
Results: Mean stereo acuity without refractive correction was 634.22 (±681.89) and with correction was 295.56 (±218.71). A statistically significant improvement was seen in stereopsis with the spectacles ($P = 0.001$), and a significant association between history of patching therapy ($P = 0.00$) and angle of deviation ($P = 0.02$) with stereopsis before the optical correction was found.
Conclusions: In refractive accomodative esotropia, stereopsis improved after wearing full optical correction. The decreased stereo acuity was associated with a history of patching therapy, as a result of the patients' late presentation in seeking care. Improvement in stereopsis is dependent on suitable treatment, like full spectacle correction and patching therapy for amblyopia in refractive accomodative esotropia. The near angle of deviation also showed a significant association with stereopsis before optical correction.

Key words: depth perception, esotropia, esodeviation, refractive error, stereoscopic vision

INTRODUCTION

Binocular single vision (BSV) is the collective use of both eyes to merge and perceive 2 separate and slightly different images seen by each eye, as one single image using sensory or motor fusion. There are 3 grades of BSV, i.e. simultaneous perception, fusion (sensory and motor), and stereopsis (depth perception) [1]. Stereopsis is a combination of two Greek words: stereo, meaning "solid", and opsis, meaning "appearance, sight". It is defined as the relative ordering of visual objects in depth, i.e. three-dimensional. It is often referred to as depth or in more general terms, three-dimensional perception obtained based on visual information from each eye in individuals with normally developed BSV [2].

The principle for measuring the stereo acuity threshold is based on the minimum detectable disparity [3]. Clinically, evaluation and measurement of stereo acuity have become an important routine screening task along with visual acuity and color vision, both for adults and younger children [4]. The unit of measurement of stereopsis is the second of arc, where 60 sec = 1 min and 60 min of arc = 1°; the smaller this value is, the better the stereo acuity. The normal value for stereo acuity is 60 sec of arc [5]. Different tests are used to measure stereopsis which include the Frisby stereo test, Titmus Fly stereo test, TNO stereo test, and Lang stereo test [6]. BSV can be normal if no manifest deviation is present or anomalous in the presence of manifest squint, when the image of an object is not projected onto the retina of both eyes [1]. It is characterized by the abnormal alignment of one eye concerning the other eye which is accompanied by abnormal ocular mobility, double vision, poor binocular visual function, abnormal head position, etc., and is one of the most frequent ocular disorders among children and adolescents [7, 8]. Based on the direction of the deviation, strabismus is divided into horizontal and vertical deviation. The horizontal deviation is further divided into 2 types: esotropia (inward deviation of eyes) and exotropia (outward deflection of eyes). Vertical deviation comprises hypertropia (upward deviation of eyes) and hypotropia (downward deflection of eyes) [9].

Esotropia or crossed eyes is characterized by an inward movement of one or both eyes which may occur with fixation at near, at distance, or both. This inward deviation may involve one eye only (constant) or may alternate between the 2 eyes (intermittent) [10]. Refractive accommodative esotropia (RAE) is one of the most commonly presented types of childhood esotropia [11]. It is an acquired convergent squint which is associated with the activation of accommodation reflex and is corrected by prescribing full hypermetropic refractive correction i.e. from +2.00 DS to +7.00 D [12].

In RAE, the uncorrected hypermetropia impels the patient to use more accommodation in order to clear the image on the retina which results an increase in convergence of both eyes [13]. Even if, the accommodative convergence to accommodation ratio (AC/A) may be normal, esotropia results if amplitude of fusional divergence is not enough to compensate for increased convergence [5]. RAE is divided into two types, fully accommodative esotropia in which eyes become fully straight for near and distance with the use of full hypermetropic correction, and the patient regains good fusion. In partially accommodative esotropia even after full correction, there is residual esotropia (usually 10Δ or more) [14].

The present study aims to measure the level of improvement of stereopsis in children having RAE after wearing their full optical correction and if prompt and suitable optical correction can reduce the adverse effects of RAE on binocular sensory function particularly stereopsis or not. The present study was also conducted to investigate the factors that affect stereo acuity in RAE patients so that their early management could be ensured and hence the reduction in stereo acuity associated with RAE can be minimized.

OBJECTIVES

1. To measure the degree of stereopsis in RAE.
2. To determine the factors that affect stereocuity.

MATERIALS AND METHODS

A cross-sectional study was done at the orthoptics department of a tertiary eye care hospital, after it was approved by the institutional review board. The sample size was 45, and a non-probability convenient sampling technique was used. Data was collected using a predesigned proforma and abided by the principles of the Helsinki Declaration. The age of subjects having RAE ranged from 4–15 years, and those who were using glasses for at least 6 months were included. Complete history, including demographic, systemic history, ocular history, family ocular history, history of patching therapy, and birth history, was taken. Visual acuity was measured using ETDRS and Cardiff Acuity cards. Squint angle was measured with the use of Hirschberg test, Prism Cover Test (PCT) and Krimsky test.

RAE is described as having less than 10 prism diopters of residual esotropia following complete hyperopic correction. Those individuals were excluded from the study who had a positive history of squint surgery, an ocular ailment (such as glaucoma, cataract or other opacity in media, optic nerve pathology), a systemic disease (such as a neurological or developmental problem), patients with mental disorders, or those who had experienced any kind of ocular trauma.

The following additional factors were also examined: age, sex, duration of misalignment (i.e., the time between the reported onset of esotropia and spectacle correction), patching hours for amblyopic patients, refractive error obtained after cycloplegic refraction, deviation at near and distance fixation with correction, extraocular muscle's movement (EOM), and stereo acuity. All the subjects in the study showed a decrease inisesotropia after hyperopic correction. The cover test was used in the orthoptic examination to determine the nature of the deviation, the objective angle by the Hirschberg test using an ophthalmoscope, and the alternative PCT was used to calculate the total angle of deviation in prism diopters. The deviation in younger children was measured using Krimsky. The Titmus Fly test was used to measure stereo acuity while wearing polaroid glasses at a distance of 40 cm.

The participant was instructed to grasp the fly's wing and name the animal that appeared to pop out the paper. The examiner confirmed the answers by flipping the book over so that stimulus was reversed. If a correct answer was received for the target before it, the disparity of that target was measured and recorded. If the response was inaccurate, it was attempted to achieve the proper response by moving backward from the target sequence. The patient's stereopsis was measured using the last accurate target found. If the patient didn't respond to the highest discrepancy, stereo acuity was recorded as zero, and for statistical analysis, a score for zero stereopsis was 6000 sec of arc. The entire process was carried out under ambient light. For descriptive data, frequencies and percentages were reported for categorical variables, while mean and standard deviation were reported for continuous variables. Using SPSS version 26.0, the paired samples t-test and independent samples t-test were used for inferential analysis. The level of significance was set at a value of P <0.05, with confidence interval of 95%.

TABLE 1

Orthoptics assessment.

Variables	Min	Max	M (±SD)
Hirschberg (objective angle)	1°	35°	13.02 (±7.80)
PCT Aided			
Near	0	70 Δ	15.31 (±16.39)
Distance	0	70 Δ	15.11 (±16.09)
Krimsky (aided)	0	55 Δ	7.93 (±14.95)

The results demonstrated that there was a statistically significant correlation between the history of patching, PCT (near), and stereo acuity without refractive correction, with t = -3.63, P = 0.001, and t = 2.34, P = 0.02, respectively. But, no statistically significant association was present between the duration of misalignment, the family history of squint, relationship with the patient, duration of patching, hours of patching, refractive error, EOM, and stereo acuity without refractive correction, as P >0.05.

TABLE 2

Comparison of stereopsis before and after glasses (n = 45).

Variable	Mean (±SD)	t (df)	P-value
Stereopsis (unaided)	634.22 (±681.89)	3.567 (44)	0.001
Stereopsis (aided)	295.56 (±218.71)		

*statistically significant P <0.05.

The results of the independent t-test showed that statistically no significant association was found between duration of misalignment, family history of squint, relationship with the patient, history of patching, duration of patching, hours of patching, range of PCT (near), refractive error, EOM, stereo acuity with refractive correction as P >0.05.

RESULTS

A total of 45 patients meeting the inclusion criteria participated in the study during a period of 4 months from October 2021 to January 2022. Both genders were included in the study, in which 55.6% (n = 25) were males and 44.4% (n = 20) were females. The mean patient's age was 8.56 (±3.327), ranging from 4 to 18 years. The mean PCT was 15.31 (±16.39) prism diopter (Δ) for near and 15.11 (±16.09) Δ for distance. See table 1 for a detailed orthoptic assessment.

The average difference between paired samples, e.g. stereopsis before and after optical correction, was found using the paired sample t-test. To evaluate any changes in the degree of stereopsis with optical correction in patients of RAE, the paired sample t-test showed a statistically significant difference in stereopsis before and after spectacle correction, t = 3.567, P <0.001 (tab. 2).

To find the influence of duration of onset of squint, history of squint among family members, amblyopia, amblyopia therapy, refractive error, extraocular movement disorder, and the degree of squint present after optical correction of the refractive error on stereoacuity outcomes in RAE, an Independent sample t-test was applied. Results are summarized in tables 3 and 4.

DISCUSSION

The purpose of the current study was to determine the degree of stereopsis and factors that influence stereopsis in patients with RAE. The Titmus Fly stereo test was used to measure stereopsis at a 40 cm distance. The Titmus Fly stereo test was inducted as a basic test on condition of contention, only the readings of this test were taken into account. The Titmus stereo test was easy to understand for children as well as for adults. Moreover, it was feasible to conduct the study with this test.

Refractive adaptation capacity along esotropia is examined as the eye's inward deflection, associated with accommodation reflex activation. By employing full cycloplegic refrac-

TABLE 3

Factors affecting stereo acuity outcomes (without refractive correction).

Variable	Mean (±SD)	t (df)	P-value
Duration of misalignment			
<2.211	689.41 (±768.11)	1.50 (42.99)	0.14
≥2.11	463.64 (±237.79)		
Family history			
Yes	777.78 (±868.58)	0.58 (10.25)	0.57
No	598.33 (±636.76)		
Relationship with patient			
First degree relative	514.29 (±279.45)	-1.19 (9)	0.26
Second degree relative	1100.0 (±1290.11)		
History of patching			
Yes	448.24 (±233.45)	-3.63 (43.0)	0.00
No	1209.09 (±1176.8)		
Duration of patching			
<1.93	746.21 (±819.44)	1.50 (43.0)	0.14
≥1.93	431.25 (±205.64)		
Hours of patching			
<1.53	791.30 (±911.0)	2.34 (42.81)	0.11
≥1.53	470.0 (±222.51)		
Refractive correction			
<4.15	552.38 (±608.78)	-0.76 (42.81)	0.45
≥4.15	705.83 (±5.50)		
PCT (near)			
<15.31	828.46 (±830.77)	2.34 (43.0)	0.02
≥15.31	368.42 (±221.24)		
EOM			
Full	700.0 (±788.22)	1.46 (41.43)	0.11
Partially restricted	472.31 (±244.88)		

EOM – extraocular muscle's movement; PCT – prism cover test.

tive adjustment, it can be eliminated with residual esodeviation of less than 8–10 prism diopters [15, 16]. RAE typically starts at the age of 2–3 years, after the stereopsis has markedly developed. Hence, according to some authors, the majority of children with RAE should have a good chance of developing binocular sensory functions if diagnosed early [15, 17]. In stereopsis, two different 2D images of the object combined to create a 3D representation of that image i.e. depth perception in the visual world around us [18].

The findings of this study suggested that the degree of stereopsis improved after wearing full optical correction in RAE patients, as both the factors (stereo acuity and refractive correction) in RAE patients were significantly related to each other as (P = 0.001) which is statistically significant. These results were supported by a Japanese study that found that the patients who were using full refractive correction and had minimal residual esodeviation at near and distance could achieve a higher level of stereo acuity [19]. Similar results were shared by another study, which showed that stereopsis becomes good (i.e. 85 sec of arc), after refractive correction in smaller deviations [12]. The study conducted in Karachi Pakistan also shared similar results stating that 7 participants exhibited weak stereopsis i.e. (340 sec of arc) so far, following refractive correction, they acquired good stereopsis i.e. (85 sec of arc) whereas 3 of them showed mild stereopsis (170 sec of arc) which was improved after wearing spectacles correction with a p-value of 0.018 [20].

Considering the elements that influence stereo acuity outcomes in RAE, results of the present study depicted that only the degree of misalignment and presence of amblyopia were significantly associated with stereo acuity without refractive correction, with P <0.05 which means stereo acuity in RAE patients is influenced by amblyopia and magnitude of constant misalignment. Duration of misalignment, family

TABLE 4

Factors affecting stereo acuity outcomes (with refractive correction).

Variable	Mean (±SD)	t (df)	P-value
Duration of misalignment			
<2.211	282.94 (±223.44)	-0.70 (18.04)	0.49
≥2.211	334.55 (±208.63)		
Family history			
Yes	217.78 (±140.87)	-1.59 (20.34)	0.12
No	315.0 (±231.63)		
Relationship with patient			
First degree relative	208.57 (±136.06)	-0.73 (5.83)	0.49
Second degree relative	275.00 (±150.00)		
History of patching			
Yes	298.24 (±199.84)	0.12 (13.44)	0.90
No	281.27 (±280.32)		
Duration of patching			
<1.93	302.07 (±212.76)	0.25 (28.43)	0.49
≥1.93	283.75 (±235.76)		
Hours of patching			
<5.13	259.13 (±212.76)	-1.14 (41.94)	0.25
≥5.13	333.64 ±2 30.22)		
Refractive correction			
<4.14	287.62 (±214.8)	-0.22 (43)	0.82
≥4.14	302.50 (±226.45)		
PCT (near)			
<15.31	333.85 (±261.42)	1.38 (43)	0.17
≥15.31	243.16 (±130.34)		
EOM			
Full	258.13 (±187.64)	-1.59 (17.01)	0.12
Partially restricted	387.64 (±267.40)		

EOM – extraocular muscle's movement; PCT – prism cover test.

history of squint, relationship with the patient, refractive error, EOM, duration of patching, and hours of patching had no statistically significant relation with stereo acuity without refractive correction, as P >0.05. This study was somewhat similar to the one conducted in Turkey, which reported that poor stereo acuity was significantly related to the presence of amblyopia [21]. Uretmen et al. concluded that stereo acuity was found to be impacted adversely by persistent misalignment observed at any visit in patients with RAE [22].

A study conducted in Pakistan showed that stereopsis was significantly linked with the angle of deviation in patients of RAE [12]. Guclu et al. concluded that due to the late presentation of patients for getting treatment, low stereo acuity was mostly associated with amblyopia. Adequate refractive correction and patching therapy during RAE were vital for the development of stereopsis. The deviation angle at near and the period of misalignment could also be inferred as a cause for poor stereoacuity [13]. According to Fawcett et al., the period of misalignment in RAE patients was correlated with fine random stereo acuity. However, in this study, no considerable association was observed between stereo acuity outcomes and duration of constant misalignment in RAE. Even though the duration of constant misalignment was assessed using the same methodology as Fawcett et al. These results were interpreted tentatively because the history given by the parents was used as a basis for this methodology [23]. If the eyes were properly aligned before or soon after the commencement of constant deviation, many researchers claimed that binocular single function (BSF) would be excellent [22]. Another study showed that the degree of deviation without correction harmed binocular vision and stereopsis in RAE. Some other factors, such as anisometropia, age of onset of deviation, period of deviation before treatment, high hypermetropia, and high AC/A, did not cause impaired binocular function [24]. Iqbal et al. accomplished the results of their study as the children with RAE had good visual acuity, ocular alignment, and BSV with Spectacles correction but their study didn't measure stereopsis in those patients [25]. Çakır et al. reported that there are certain risk factors for the development of stereopsis, such as inferior oblique overaction, best corrected visual acuity in amblyopia, and alternation of fixation in patients with RAE and amblyopia [26]. Similar results were shared by Mulvihill et al.; however, they did not emphasize risk factors [11].

CONCLUSIONS

It was concluded from the study that stereo acuity in RAE was improved after wearing optical correction. To restore orthotropia at all fixation distances, early optical correction of underlying refractive error was essential. It was also important for the stability of stereopsis, and is crucial for the stability of stereopsis. It was determined that constant eye misalignment, even after wearing spectacles, posed a risk factor for poor stereo acuity. Hence, to reduce the deleterious effects of ongoing ocular misalignment on stereopsis, it was important to ensure that ortho position was achieved and maintained by prescribing appropriate optical correction. It was also found that the presence of amblyopia was associated with poor stereo acuity, therefore, treatment of amblyopia was necessary for the progress of good stereopsis. To achieve better results, parents should be reminded of the significance of consulting an eye physician at the start of symptoms and encouragement of children to wear their glasses at all times, promptly to reduce the severe effects of constant deviation on stereopsis in RAE.

CORRESPONDENCE
Farah Naheed, optometrist, B.Sc.
Al-Shifa Trust Eye Hospital
Jhelum Road, Rawalpindi, Pakistan
Phone: +923407755498
E-mail: gurria98naheed@gmail.com

ORCID
Rabia Jabeen – ID – http://orcid.org/0009-0005-7826-1520
Maryam Firdous – ID – http://orcid.org/0000-0001-7352-4313
Farah Naheed – ID – http://orcid.org/0000-0003-2137-3917
Saif Ullah – ID – http://orcid.org/0000-0003-3254-5585
Rimsha Tanveer Kiyani – ID – http://orcid.org/0009-0002-8684-5145
Sadaf Qayyum – ID – http://orcid.org/0000-0002-7937-5184

Cite as: Jabeen R, Firdous M, Naheed F et al. Effect of optical correction on the stereopsis of patients with refractive accommodative esotropia and factors affecting it. Ophthatherapy. 2026; 13(2): A0008.

References

1. Rowe FJ. Clinical Orthoptics. 1st ed. Wiley, 2012.
2. Howard IP, Rogers BJ. Binocular Vision and Stereopsis. Oxford University Press, 1996.
3. Borish's clinical refraction. 2nd ed. Benjamin WJ, Borish IM (eds.).: Butterworth Heinemann/Elsevier, St. Louis Mo 2006.
4. Mohamed I, Naveed F, Burhan T et al. Comparision of streopsis in patients with fully and partially accommodative esotropia. Ophthalmology Pakistan. 2019; 9(3): 18-22.
5. Salmon JF, Kanski JJ. Kanski's clinical ophthalmology: A systematic approach. Elsevier, Edinburgh 2020.
6. Von Noorden GK, Campos EC. Binocular vision and ocular motility: theory and management of strabismus. 6th ed. St. Louis, Mo., Mosby; 2002. 653 p.
7. Rajasekaran R, Ramesh MK, Balagopal A et al. Prevalence of various types of strabismus among patients attending a Tertiary Eye Care Hospital at tiruchirappalli. Jemds. 2018; 7(52): 5484-7. http://doi.org/10.14260/jemds/2018/1213.
8. Fieß A, Elflein HM, Urschitz MS et al. Prevalence of strabismus and its impact on vision-related quality of life. Ophthalmology. 2020; 127(8): 1113-22. http://doi.org/10.1016/j.ophtha.2020.02.026.
9. Blair E, Smithers-Sheedy H; The Australian Cerebral Palsy Register Group. Strabismus, a preventable barrier to social participation: A short report. Develop Med & Child Neuro. 2016; 58(S2): 57-9. http://doi.org/10.1111/dmcn.13020.
10. Kennedy SA, Noble J, Wong AMF. Esotropia. CMAJ. 2012; 184(11): 1279. http://doi.org/10.1503/cmaj.111566.

11. Mulvihill A, MacCann A, Flitcroft I et al. Outcome in refractive accommodative esotropia. Br J Ophthalmol. 2000; 84(7): 746-9. http://doi.org/10.1136/bjo.84.7.746.
12. Iqbal I, Saeed R, Bajwa JA et al. Stereopsis in patients of refractive accomodative Esotropia. AOVS. 2019; 9(3): 66-9. http://doi.org/10.15406/aovs.2019.09.00348.
13. Guclu H. Prognostic factors for stereopsis in refractive accomodative esotropia. Pak J Med Sci. 2015; 31(4): 807-11. http://doi.org/10.12669/pjms.314.7465.
14. Olitsky SE, Chan EW, Farzavandi S. Strabismus: Accommodative esotropia. American Academy of Ophthalmology. 2016. https://www.aao.org/education/disease-review/strabismus-accommodative-esotropia.
15. Wilson ME, Bluestein EC, Parks MM. Binocularity in Accommodative Esotropia. J Pediatr Ophthalmol Strabismus. 1993; 30(4): 233-6. http://doi.org/10.3928/0191-3913-19930701-04.
16. Swan KC. Accommodative esotropia long range follow-up. Ophthalmology. 1983; 90(10): 1141-5. http://doi.org/10.1016/s0161-6420(83)34415-8.
17. Köse S, Pamukçu K, Haznedaroĝlu G. Qualitative and quantitative evaluation of binocular function in accommodative esotropia using pattern reversal visual evoked responses (VER). Neuro-Ophthalmology. 1993; 13(5): 275-9. http://doi.org/10.3109/01658109309038162.
18. Poggio G. The analysis of stereopsis. Annu Rev Neurosci. 1984; 7(1): 379-412. http://doi.org/10.1146/annurev.neuro.7.1.379.
19. Matsuo T, Yamane T, Fujiwara H et al. Predictive factors for long-term outcome of stereoacuity in Japanese patients with pure accommodative esotropia. Strabismus. 2005; 13(2): 79-84. http://doi.org/10.1080/09273970590935084.
20. Azam S, Talpur AH, Bukhari S et al. Stereopsis in accommodative esotropia at Al-Ibrahim Eye Hospital, Karachi, Pakistan. Acta Scientific Ophthalmology. 2021; 4(4): 85-8.
21. Berk AT, Koçak N, Ellidokuz H. Treatment outcomes in refractive accommodative esotropia. J AAPOS. 2004; 8(4): 384-8. http://doi.org/10.1016/j.jaapos.2004.02.001.
22. Uretmen O, Kose S, Oztas Z et al. Factors influencing stereoacuity in refractive accommodative esotropia. Can J Ophthalmol. 2007; 42(4): 600-4. http://doi.org/10.3129/i07-100.
23. Fawcett S, Leffler J, Birch EE. Factors influencing stereoacuity in accommodative esotropia. J AAPOS. 2000; 4(1): 15-20. http://doi.org/10.1016/s1091-8531(00)90006-5.
24. Bayar SA, Ozturker ZK, Ulas B et al. Factors affecting binocular sensorial function in accomodative esotropia. Beyoglu Eye J. 2021; 6(3): 166-72. http://doi.org/10.14744/bej.2021.77598.
25. Iqbal MS, Hussain SA, Qazi ZU. Refractive accommodative esotropia; TPMJ. 2013; 20(02): 301-7. http://doi.org/10.29309/tpmj/2013.20.02.630.
26. Çakır B, Bursalı Ö, Özmen S et al. Factors influencing stereopsis in patients with both refractive accommodative esotropia and Amblyopia. Int Ophthalmology. 2018; 39(6): 1263-7. http://doi.org/10.1007/s10792-018-0937-8.

Authors' contributions:
Rabia Jabeen performed the data collection and analysis, and wrote the original draft of the manuscript.
Farah Naheed did the data collection, writing-reviewing, and editing of manuscript.
Rimsha Tanveer Kiyani did the data curation and data analysis.
Maryam Firdous, Saif Ullah, and Sadaf Qayyum supervised the project and critically review the manuscript. All authors read and approved the final manuscript.

Conflict of interest:
None.

Financial support:
None.

Ethics:
The content presented in the article complies with the principles of the Helsinki Declaration, EU directives and harmonized requirements for biomedical journals