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Original Article

Percutaneous Closure of Patent Ductus Arteriosus in Children Using ADO I and ADO II Devices: A Thirteen Year Single Centre Experience

Çocuklarda Perkütan Yöntemle ADO I ve ADO II Cihazları Kullanılarak Patent Duktus Arteriosus Kapatılması: On Üç Yıllık Tek Merkez Deneyimi

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ABSTRACT

Objective: Transcatheter closure of patent ductus arteriosus (PDA) has taken its place as the first choice in the treatment of PDA thanks to the development of new devices and techniques. In this study, we present our cases with PDA closed with Amplatzer duct occluder I (ADO I), Amplatzer duct occluder II (ADO II) and discuss the efficacy and safety of transcatheter PDA closure with these devices in children.

Method: Between January 2010 and January 2023, a total of 373 patients underwent PDA closures using ADO I (n=40), and ADO II (n=333) devices in the Pediatric Cardiology Clinic of our hospital and PDA closure was successfully performed in 370 patients. These cases were analysed retrospectively.

Results: The mean age of our patients was 3 (0.2-17) years. The mean narrowest diameter of the PDA was 2.48±0.80 mm. Median procedure and fluoroscopy times were 55, and 11 minutes, respectively. The procedure was successful in 99.1% of the cases. PDA was successfully treated in 387 patients using ADO I (n=39), ADO II (n=331) devices. Minimal residual shunt was detected as a minor complication only in 7 patients in the acute phase. In 4 of these 7 patients, residual shunt disappeared completely in the follow-up period, but it persisted in 3 patients. Major complications in our study were device embolisation in 2 patients who underwent ADO I and infective endocarditis that developed in 1 patient 2 weeks after the procedure. In our patient with device embolisation, the device was tried to be removed with the help of a snare, but it failed, so it was surgically removed and the PDA was closed surgically. In our case with infective endocarditis, the device was surgically removed and the PDA was surgically closed. In one patient, the mean pulmonary artery pressure measured during the procedure was found to be high with 29 mmHg, but the procedure was continued because the pulmonary vasoreactivity test was positive. In the procedure performed with ADO I device, the PDA was closed by opening the first disc without releasing the device, but the procedure was not continued because the patient developed desaturation.

Conclusion: Transcatheter PDA closure can now be successfully performed in many centres. In this study, we evaluated the cases of PDA closure performed with ADO I and ADO II devices, in the last 13 years. As a result of our study, in accordance with the literature data, we have shown that transcatheter PDA closure using ADO I, ADO II devices is an effective and safe method with low complication rates in children.

Keywords: Patent ductus arteriosus, Amplatzer duct occluder, percutaneous closure, pediatric

ÖZ

Amaç: Transkateter yöntemle patent ductus arteriosus (PDA) kapatılması yeni cihaz ve tekniklerin gelişimi ile birlikte tedavide ilk seçenek olarak yerini almıştır. Bu çalışmada Amplatzer dukt okluder (ADO) ve Amplatzer dukt okluder II (ADO II) kullanılarak kapatılmış olgularımız sunulmuş, çocuklarda bu cihazlarla PDA kapamanın etkinlik ve güvenilirliği tartışılmıştır.

Yöntem: Hastanemizçocuk kardiyoloji kliniğinde Ocak 2010-Ocak 2023 tarihleri arasında toplam 373 hastaya (40 ADO, 333 ADO II) cihazı uygulanmış, 370 hastada PDA kapama başarıyla yapılmıştır. Bu olgular retrospektif olarak incelenmiştir.

Bulgular: Hastalarımızın ortanca yaşı 4,3 yıl (2 ay-17 yaş) idi. PDA en dar çapı ortalama 2,45±0,80 mm idi. Ortalama işlem ve floroskopi süreleri sırasıyla 55 ve 11 dakika idi. Olguların %99,1'inde işlem başarılı olmuştur. Başarılı olunan 370 hastanın 39'unda ADO, 331'inde ADO II cihazı kullanılmıştır. Minör komplikasyon olarak yalnızca 7 hastada akut dönemde minimal rezidüel şant saptanmıştır. Bu 7 hastanın 4'ünde takipte rezidüel şant tamamen kaybolmuş 3'ünde ise minimal düzeyde devam etmiştir. Çalışmamızda majör komplikasyonlar ADO II uygulanan 2 hastada görülen cihaz embolizasyonu ve 1 hastamızda işlemden 2 hafta sonra gelişen enfektif endokardit idi

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Cihaz embolizasyonu gelişen olgumuzda cihaz snare yardımıyla çıkarılmaya çalışılmış ancak başarısız olunması üzerine cerrahi olarak çıkartılmış ve PDA cerrahi yöntemle kapatılmıştır. Enfektif endokardit olan olgumuzun cihazı cerrahi olarak çıkarılmış ve PDA cerrahi olarak kapatılmıştır. İşlem sırasında bir hastada ortalama pulmoner arter basıncı yüksek (29 mmHg) ölçülmüş, ancak pulmoner vazoreaktivite testi pozitif olduğu için işleme devam edilmiştir. ADO I ile uygulanan işlemde cihazı çıkartmadan önce ilk disk açılarak PDA kapatılmış, ancak hastada desatürasyon geliştiğinden işleme devam edilmemiştir.

Sonuç: Transkateter PDA kapatma artık birçok merkezde başarıyla uygulanabilmektedir. Biz de bu çalışmada son 13 yılda ADO I, ADO II cihazlarıyla gerçekleştirdiğimiz PDA kapatma olgularını değerlendirdik. Çalışmamızın sonucunda literatürle de uyumlu olarak, çocuklarda transkateter yöntemle ADO I, ADO II embolizasyon cihazları kullanılarak yapılan PDA kapamanın düşük komplikasyon oranıyla etkili ve güvenli bir yöntem olduğunu göstermiş olduk.

Anahtar kelimeler: Patent duktus arteriosus, Amplatzer dukt okluder, perkütan kapatma, pediatrik

INTRODUCTION

Patent ductus arteriosus (PDA) is located between the left pulmonary artery and the anterior descending aorta in the intrauterine period and its presence is necessary to receive oxygen from the placenta during the fetal period. After birth, as the infant's respiratory system is activated, the ductus arteriosus is expected to close, first functionally and then anatomically with fibrous replacement of the ductal tissue[1]. When the PDA does not close, an open connection remains between the left pulmonary artery and the anterior descending aorta with resultant increase in the left ventricular workload and the risk of heart failure[2]. In addition, pulmonary hypertension may develop with an increased risk of mortality and morbidity in the long term[3]. Transcatheter closure of PDA is an interventional procedure that does not require surgical intervention and is currently the firstly preferred treatment option. PDA closure was first performed by Porstmann et al.[4] in a 17 year-old female patient using an Ivalon plug. In the following years, Rashkind and Cuaso[5] used a polyurethane foam-coated disc umbrella, and in our country, treatment with the Rashkind umbrella was initiated in the early 1990s, and then oscillation-controlled coils were used for the occlusion of PDA. While a controlled oscillation coil can be used for a small diameter PDA, devices such as the Amplatzer duct occluder I (ADO I) and Amplatzer duct occluder II (ADO II) may be preferred for the management of a PDA with a larger diameter. ADO I and II are preferred devices because of their ease of surgical application, repositioning and low migration rate[6].

In this study, we aimed to observe our mid-to long-term clinical experience with transcatheter PDA closure using ADO I and ADO II devices and to evaluate the efficacy and safety of transcatheter PDA closure with these two devices.

MATERIALS and METHODS

A retrospective evaluation of 373 patients with PDA hospitalised in our clinic between 2010 and 2023, and underwent transcatheter closure of PDA. The procedure details of these patients were obtained from the hospital archives. The written consent was obtained from the families of the patients included in the study.

The study was conducted in accordance with the Helsinki Declaration's standards and was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee (decision number: 2023/514/258/26, date: 27.09.2023).

Using transthoracic echocardiography, the defect was evaluated in detail through the parasternal short axis and suprasternal windows and its morphology and dimensions were determined. Patients with irreversible pulmonary vascular disease (Eisenmenger syndrome) or high pulmonary/systemic pressure and resistance ratios did not undergo closure and were excluded from the study.

Devices

The ADO I and II devices (AGA Medical Corporation, Golden Valley, Minnesota, USA) are low-profile, self-expanding occluders consisting of a mushroom-shaped 0.0004-0.0005 inch nitinol wire mesh. They consist of a metal rigid disc on the outside and a cylindrical main body containing polyester fibrils inside. The cylindrical body is asymmetrical and the proximal part is smaller (Figure 1). The ADO I device is a low-profile device consisting of a mushroom-shaped nitinol wire mesh. It consists of a distal retention disc that can self-expand and attach to the ampulla and tubular parts that occlude the ductus proximally. The body length of the device varies between 5-8 mm. The diameter of the retention disc is 4 mm larger than the body diameter[7]. The ADO II device, which was developed later, consists of two equal sized discs and a thin waist in the middle. This device has a waist diameter of 3-6 mm and a length of 4-6 mm and is designed for closure of ducts with a diameter smaller than 6 mm (Figure 2). Since the ADO II device does not contain filler, it can be placed with smaller diameter delivery catheters[8,9]. ADO I and ADO II devices are very suitable for the closure of conical shaped ducts.

The PDA can be closed by antegrade (arterial) or retrograde (venous) approach. In the retrograde

approach, it is necessary to insert a second arterial catheter for angiographic control after placement of the device. The advantage of the antegrade approach is that every stage of the procedure can be controlled by injections through the arterial catheter. While the ADO II device can be applied using both venous and arterial access, the ADO I device can only be applied through the antegrade approach[10].

In our study, our choice of venous or arterial approach was based on the echocardiographic and angiographic shape of the PDA, the patient's age, weight and the diameter of the descending aorta.

Catheterisation

All patients received prophylaxis for infective endocarditis and dissociative anaesthesia with midazolam and ketamine before the procedure. Local anaesthesia was also applied to the puncture site. Firstly, cardiac catheterisation was performed to determine haemodynamic variables. Depending on the height and weight of the patient, 4F, 5F and/or 6F sheaths were inserted into the right femoral vein and/or artery using Seldinger percutaneous technique[10]. After administration of heparin at a dose of 50-100 U/kg for heparinisation, systolic, diastolic and mean arterial pressures were measured with a multipurpose catheter and blood gases were obtained from the superior vena cava and pulmonary artery. Blood gases obtained from pulmonary artery and right ventricle were analysed for patients to be intervened by retrograde route. Pulmonary blood flow/systemic blood flow (Qp/Qs) ratio was determined according to Fick's principle of cardiac output measurement[11]. As a standard procedure, cardiac catheterisation was performed with the patient lying in 90 degrees left lateral decubitus position and right anterior oblique position. Aortography was performed with a non-ionic opaque substance at a dose of 1-1.5 mL/kg (maximum 30 mL) using a pigtail catheter and the ampulla, narrowest point and length of the ductus were measured and typing of PDA was performed according to the angiographic method proposed by Krichenko et al.[12] (Figure 3).

Figure 1. Amplatzer duct occluder I

Figure 2. Amplatzer duct occluder II

Percutaneous Closure Procedure

Two different devices, ADO I, and II were used for percutaneous closure. The choice of the device was based on factors such as the width of the ampulla on the aortic side of the duct on aortography, its narrowest diameter and length.

The closure procedure was performed under sedation. General anaesthesia was not preferred except

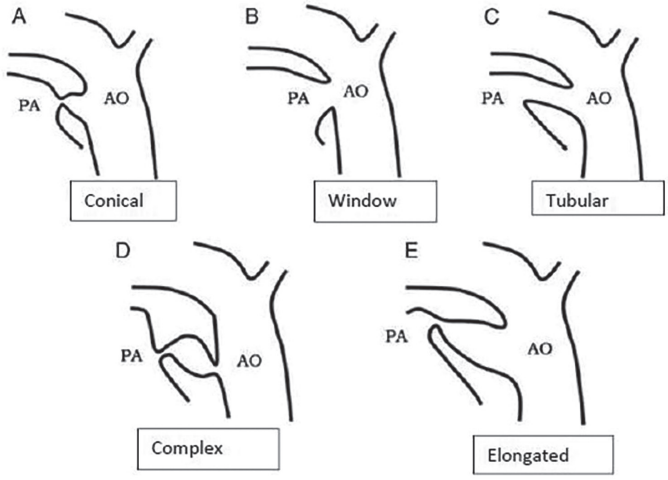

Figure 3. Angiographic classification of patent ductus arteriosus

in rare cases where the patient was resistant to medical anaesthetic drugs used for sedation and was mobile enough to threaten the safety of the procedure[13]. Intravenous heparin at a dose of 50-100 units/kg was given to all patients during the procedure.

There are no hard and fast rules for which patients ADO II or ADO I devices should be preferred[14]. However, we decided on the device to be used by measuring the diameter and length of the ductus, the width of the bulb, and the diameter of the descending aorta. For example, in patients with large PDA, if the PDA was conical and not very long, ADO I device was preferred. In patients with smaller PDA, ADO II device was preferred if the diameter of the descending aorta was appropriate (so that the device would not cause stenosis). In addition, ADO II device can also be implanted via the retrograde route, in cases where the pulmonary artery does not pass through the PDA to the aorta allowing the implantation of this device via the retrograde route. Therefore, we primarily preferred the ADO II device in small or medium-sized defects or in cases where antegrade passage could not be achieved.

In the transvenous approach, a multipurpose catheter with a sheath was inserted percutaneously through the right femoral vein and artery and a 150 cm-0.035 inch guidewire was then advanced percutaneously by way of the ductus through the inferior vena cava, right atrium, right ventricle and pulmonary artery to the descending aorta. The guidewire was then replaced with a new 260 cm-0.035 inch guidewire and the Amplatzer TorqVue LP delivery system was guided from the ductus to the descending aorta. Firstly, the disc on the aortic side of the device and then the disc on the pulmonary artery side were opened. In the transarterial approach, only the sheath was placed in the right femoral artery. Using a 150 cm-0.035 inch guidewire, the ductus was passed through the descending aorta with the Judkins right catheter and the main pulmonary artery was reached. The guidewire was replaced with a 260 cm-0.035 inch guidewire and under the guidance of this wire, the Amplatzer TorqVue LP delivery system was passed from the ductus to the main pulmonary artery. Firstly, the disc of the device on the pulmonary artery side and then on the descending aorta side were opened. Control aortography and transthoracic echocardiography were performed to check the location of the device, the opening status of the discs and the residual shunt. Control angiography was performed using a separate catheter passed through the aorta in cases with antegrade closure, whereas in retrograde cases, it was performed using the loading catheter of the device. Afterwards, if the device was in the appropriate position, it was released from the delivery system, inserted into the ductus and the procedure was terminated. Then, the patients were taken to the ward and monitored and the puncture sites were checked. Control echocardiography was performed one day later. Two-dimensional and colour Doppler echocardiograms were obtained to evaluate residual shunt, right-left pulmonary artery and stenosis of the descending aorta, ventricular function, and valvular regurgitation. Patients with no complications were discharged. Patients were evaluated clinically and echocardiographically at the 1st, 3rd, 6th, and 12th months within the first year after percutaneous closure, then followed up annually.

Statistical Analysis

Statistical analysis of the data was performed using "SPSS 18.0" statistical software. Kolmogorov-Smirnov test was performed to check for the normal distribution of the numerical data. Since all of the data in our study did not fit the normal distribution, non-parametric tests (Mann-Whitney U) were preferred. In addition, chi-square analysis was used to compare categorical data. The level of statistical significance was determined as $p<0.05$. The results obtained by these analyses were evaluated and statistically significant differences and correlations were determined.

RESULTS

In the last 13 years, transcatheter closure of PDA was attempted in a total of 373 patients using ADO I and ADO II devices in our clinic. The procedure was successful in 371 (99.5%) of these patients. In 2 patients in whom ADO I was used, the device embolized to the aorta in one patient and to the femoral artery in the other when the device was released. In the patient with device embolisation in the femoral artery, the narrowest part of the PDA was measured to be 3.9 mm and a 3x4 mm ADO I device was selected for this patient. The device embolized the right femoral artery, then it was trapped in the iliac artery bifurcation, but it was successfully removed from the body using a snare catheter. The PDA of this patient was subsequently closed surgically. In the patient with device embolisation of the aorta, the narrowest part of the PDA was measured as 2.5 mm and a 3x4 mm ADO I device was selected. The device was tried to be removed using a snare catheter but the procedure failed. The embolized device was surgically removed and the PDA was surgically closed simultaneously.

Five patients (1.3%) had previously undergone surgical PDA ligation but had residual PDA. Since an atrial septal defect of more than 8 mm was detected in the transthoracic echocardiographic evaluation of 4 patients whose PDA was closed with ADO II, simultaneous atrial septal defect device embolisation together with atrial septal defect closure was performed in these patients. In 3 patients whose PDA was closed with ADO II, mild stenosis was detected in the left pulmonary artery on transthoracic echocardiographic evaluation. In the follow-up of these patients, the stenosis completely resolved within the first 6 months. The median age of the patients was 3 (0.2-17) years and the median PDA diameter was 2.4 mm (1.1-6.5). The average follow-up period was 5 (0.5-13) years. Our study population consisted of 145 (38.8%) male and 228 (61.2%) female patients with a female/male ratio of 1.57. The median pulmonary artery pressure was 16 (13-29) mmHg. Our study patients had conical (n=259; 69.4%), tubular (n=108; 29%), window-shaped and/or elongated ductus, (n=6; 1.6%), and PDA was closed using ADO I device in 40 (10.7%) and ADO II device in 333 (89.3%) patients. The mean duration of fluoroscopy was 8.8 (4.8-26.7) minutes. The median (range) values for Qp (6.9:3.6-34.9), Qs (4.3:1.2-20.9), Qp/Qs (1.5:0.81-6), pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) (0.08:0.01-2.15), while median (range) PVR (1.5:0.2-8.8 Wood units), SVR (16.5:2.78-63.9 Wood units) were as indicated.

Minimal residual shunt was present in 7 (1.8%) patients in the early postoperative period. However, minimal residual shunt persisted in only 3 (0.08%) of these patients and the shunt disappeared in the remaining 4 (0.1%) patients.

When comparing patients in terms of the devices used, the average PDA diameter of patients who had ADO I device was statistically significantly longer than those who had ADO II device (median values of 3.2 mm and 2.2 mm, respectively; p<0.001). However, any significant intergoup differences were not observed in terms of age, weight, PVR/SVR ratio, Qp/Qs ratio, mean pulmonary artery pressures, fluoroscopy time, and duration of the procedure among patients using different devices (p>0.05). Transcatheter closure was performed using the antegrade route (venous) in 103 and the retrograde route (arterial) in 270 patients. The demographic and procedural data of the patients is summarized in Table 1.

Thrombosis developed at the access site in 6 patients. In only 1 of these 6 patients, thrombosis did not regress despite heparin treatment and recombinant tissue plasminogen activator treatment was required. Thrombosis completely regressed in this patient after treatment. All patients who developed thrombosis were patients who underwent arterial intervention.

In one male patient, 2 weeks after the procedure was successfully performed, high fever and deterioration in general condition were observed. Transthoracic echocardiography revealed an increase in echogenicity of the device which had not been seen before, and device-related infective endocarditis was considered and antibiotherapy was started. However, despite

Table 1. Demographic and procedure information

n	373
Success rate	371/373 (99.5%)
Age, median	3 (3.5 months-17 years)
Gender (male/female)	145/228 (1.57)
Follow-up duration, median	5 (5 months-13 years)
PDA narrowest diameter, median	2.4 (1.1-6.5 millimeters)
ADO I device, n (%)	40 (10.7%)
ADO II device, n (%)	333 (89.3%)
Fluoroscopy duration, median	8.8 (4.8-26.7 minutes)
Qp/Qs, median	1.5 (0.81-6)
PVR/SVR, median	0.08 (0.01-2.15)
ADO I vs ADO II PDA diameter, median	3.2 vs. 2.2 millimeters, p<0.001
Mean pulmonary pressure, median	16 (13-29 mmHg)
Antegrade approach, n (%)	103 (27.6%)
Retrograde approach, n (%)	270 (72.4%)

n: number, PDA: Patent ductus arteriosus, ADO I: Amplatzer duct occluder I, ADO II: Amplatzer duct occluder II, Qp: Pulmonary flow, Qs: Systemic flow, PVR: Pulmonary vascular resistence, SVR: Systemic vascular resistance

intensive treatment, the patient's febrile episodes did not regress and his general condition deteriorated, so surgical removal of the device was decided. After the device was surgically removed and the defect was closed, the patient's fever decreased and his general condition improved.

DISCUSSION

Complications such as neurodevelopmental adverse effects, pneumothorax secondary to surgery, development of hemorrhagic complications and infection observed after surgical closure of the PDA have led clinicians to search for alternative treatment methods, and transcatheter closure of PDA has taken the first place among treatment options as a minimally invasive procedure[15]. Closure of all haemodynamically significant PDA has been recommended[16]. Percutaneous transcatheter closure is recommended as the first-line treatment most suitably for the conical type PDA.

Over time, simplification of percutaneous transcatheter closure system, delivery of small-caliber PDA occluders and the development of innovative systems that allow repeated trials before the device is released have popularized the transcatheter method of duct closure. In our study, ducts were closed with 99.5% success by transcatheter method. PDA closure with the ADO was firstly introduced in 1997. The main criterion for device selection is the diameter and morphology of the ductus. ADO I and ADO II devices are very suitable for closure of conical and some tubular shaped ducts.

In a study evaluating 389 patients for transcatheter closure of the PDA without using arterial access, Cook® detachable coil was used in 288 and ADO I in 101 patients and patients were followed up for an average of 1 year after the closure[17]. In the ADO I group, venous access had been successful in 82% of these patients. Reintervention was necessary in two patients due to device embolisation. Ductal closure with ADO I was performed in 2 patients who developed embolisation. Unlike this study, which included a similar number of patients as our study, we preferred both antegrade and retrograde access. Our choice of venous or arterial approach was based on the echocardiographic and angiographic morphology of the duct.

As a major complication, the authors reported device embolisation in a comparable number of cases as in our study and the patients who underwent closure with ADO I developed embolisation as in our study[17]. Since arterial intervention was not performed in the above-mentioned study, thrombosis was not detected unlike our study. Since it is difficult to perform a control angiography by placing another catheter in the artery in cases where the retrograde route is used and because of the risk of embolisation, it is more preferable to use the antegrade route in eligible patients.

In a study from Italy, ADO I and II devices were used in the patient group with a mean PDA diameter of 3.2±1.2 mm (1.8-9 mm)[18]. Complete occlusion was achieved at a rate of 77.8% at 24 hours, 92.6% at 1 month and 94.4% at 23±12 months. It was reported that PDA morphology and Qp/Qs ratio did not affect the development of residual shunt or complete closure success rates. Long-term follow-up showed a higher occlusion rate in the ADO group[19]. When compared with our study, demographic characteristics and mean PDA diameters of the patients were similar in both studies. Similar to the Italian study, ductus morphology and Qp/Qs ratios had no effect on achievement of complete occlusion in our study.

In the follow-up of percutaneously closed PDAs, residual shunts may sometimes be observed and interventional treatment may be required for these residual shunts. In cases with a clinically significant residual shunt, a second closure with a coil or another device may be required which may increase the complication rates[20,21]. It should be considered that the anatomy and shape of the ductus may have altered in previously operated patients, so current attempts to close PDA should be performed accordingly. In our 3 patients with residual shunt, since the amount of residual shunt was found to be very small and haemodynamically insignificant based on the results of clinical and transthoracic echocardiographic evaluation, any re-interventional procedures were not performed and the patients were continued to be followed up clinically.

In our patients, our procedure and fluoroscopy times were similar to the literature, but we achieved higher mean occlusion rate (99.5%) using ADO I and ADO II devices. However, we prefer ADO II device in PDAs with a diameter <2.5 mm, provided that it does not cause stenosis in the descending aorta or pulmonary artery. Compared to the ADO I, the ADO II device has been used more frequently because it has a lower risk of aortic protrusion, ensures closure of almost all PDA types, and it can be used with a smaller delivery sheath as in most of our cases where ductal diameter was <5 mm. In recent years, the ADO Piccolo device, which has

flatter retention discs and a thicker waist compared to currently used occluders has been produced for the management of much smaller PDAs[22]. It can be safely applied in small PDAs with insufficient ampullas[23]. In our study, patients whose PDAs were closed with the ADO Piccolo device were not included in our study because data entry was performed afterwards. The ductuses of these patients were successfully closed and no complications developed during the procedure.

Although transcatheter closure of PDA is safe and effective, various complications such as haemolysis[24], embolisation[25], infective endocarditis[26] and narrowing of adjacent vessels may occur. In patients whose PDAs were closed by transcatheter method using different devices, major complications (significant haemolysis, infective endocarditis, device embolisation) and minor complications (mild narrowing of the descending aorta, mild narrowing of the origin of the left pulmonary artery) may be observed[27]. In a multicentre study conducted by Pass et al.[28] in the USA, PDAs of 484 patients with a mean age of 1.8 years were closed with ADO I and II devices. The major complication rate was found to be 2.3% at one year follow-up. Eighteen out of 484 (0.3%) patients had vascular complications and/or blood loss requiring transfusion. In 2 patients in our series, the ADO II device embolised to the descending aorta and femoral artery immediately after the procedure. Pulmonary artery pressure was not very high in these patients. Therefore, we thought that embolisation was related to the small diameter of the defect. In one of our patients, febrile episodes and deterioration of general health condition developed 2 weeks after the procedure, and device-associated infective endocarditis was diagnosed after transthoracic echocardiographic evaluation of the patient revealed an increase in device echogenicity that had not been previously present. In this patient, we perfectly applied prophylactic measures against the development of infective endocarditis and sterile techniques during procedures. Therefore, we found no etiology to explain the development of infective endocarditis.

In the study conducted by Gruenstein et al.[29] in 2017 with 436 patients in which they experienced PDA closure with ADO II, patients aged between 6 months and 18 years, and those with a ductal diameter <5.5 mm were included in the study. The gender (Male: 120-63%, Female: 72-38%), and mean age (2.5±4.5 years) of the patients, type of PDA (conical 73-48%, tubular 31-16%) were similar to our study. Unlike our study, the rate of elongated type PDA was close to 20% (n=38). Antegrade access had been performed in 62% (n=128) of the patients and a significant decrease in fluoroscopy time was detected in the use of retrograde access (11.6 66.3 min. vs. 15.2 69.1, min. p=0.0001). Device embolisation developed in one patient and the device was removed by snare method. In 9 patients, the procedure was not continued because of protrusion into the left pulmonary artery or aorta before the device was left *in situ*. In two patients, residual shunt persisted during the post-procedural follow-up period. Residual shunt of their patients had been closed at follow-up, while the PDA of the other patient was closed again with coil embolisation in the first year of follow-up and the shunt was repaired. In our study, we observed that mild stenosis of the left pulmonary artery detected in post-procedural transthoracic echocardiography in three patients and continuous-wave Doppler ultrasound measurement of Δ17 mmHg in the arcus aorta after transcatheter closure in one patient were completely normalised during follow-up.

In the year 2013 Liddy et al.[30] performed a PDA closure study using Amplatzer duct occluders ADO I and ADO II on 177 patients with a mean age of 3.3 years and the mean PDA diameter of 2.5 mm. One hundred and twelve patients (63.3%) with conical type ductuses underwent PDA closure using ADO I (n=89; 50.9%), or ADO II (n=59; 33.3%) devices. Residual shunt was observed in 2 patients in the first 48 hours after the procedure. The residual shunts of these 2 patients disappeared completely in 6 month follow-up. Retrograde approach was used in 60% of the patients who underwent the procedure using ADO II device. Fluoroscopy time was shorter in patients who had undergone the procedure using the retrograde approach (3.7 vs. 5.0 min., p=0.0068). Protrusion developed in 7 (3.9%) patients using ADO II and in 10 (5.6%) patients using ADO I. Device embolisation developed in two patients. There was no difference in the rates of embolisation, residual shunt and protrusion in patients who had undergone PDA closure using retrograde or antegrade route. Compared to the study performed by Liddy et al.[30], post-procedural residual shunt was seen more frequently (n=8) during early postoperative period, but it was similarly observed in only three patients during the follow-up period since the residual shunts in our study were not found to be haemodynamically significant, any re-intervention was not performed. The types of PDA repaired, retrograde approach, and embolisation rates, fluoroscopy times were comparable to those reported by Liddy et al.[30].

In a study conducted by Baykan et al.[31] in Erciyes University, 379 patients, with a mean age of 18 months

(6 months-6 years) had conical (n=182), tubular (n=174), elongated (n=2), window-type (n=21) PDAs For the PDA closure, ADO I (n=149), ADO II (n=149) devices and Cook® coils (n=179) had been used in respective number of patients. Arterial route was used in 257 and venous route in 122 patients. Device embolisation developed as a major complication in only 5 patients. The patients who had developed device embolisation weighed less than 2000 grams. Our study was demographically different from the study of Baykan et al.[31] and compatible with the literature. Although it was similar to our study in that mostly arterial interventions had been performed, the rate of major complications was lower in our study.

Eight years ago Yılmazer et al.[32] used different occluder types in 82 patients in our centre, and PDAs of 291 new patients were closed during this period. Despite a significant increase in the number of patients treated, only one patient had device embolisation as a major complication during this period and the device was surgically removed. It is remarkable that as experience gained by the clinical team, minor complications were not seen except for 2 new patients with haemodynamically insignificant shunts.

Our results have shown that transcatheter PDA closure is an effective and safe method with low complication rates in children. In our study, the procedure was performed in a total of 370 patients with a success rate of 99.1 percent. Device embolisation occurred in only two patients and surgical intervention was required in these patients. Embolisations were observed in patients in whom the ADO I device was used. The ADO II device allows the closure of more challenging anatomical structures due to its advantages of using the retrograde route. Careful patient selection and meticulous planning of the procedure is important in patients at risk of embolisation.

Very scarce number of (1.8%) patients had minimal residual shunts in the acute period after closure. Except for a few patients, almost all of the residual shunts in the acute period were closed. These results support the efficacy and success of transcatheter PDA closure. Major complications such as device embolisation and infective endocarditis were rarely seen (0.8%). The case of infective endocarditis was treated by surgical removal of the device. Such rare complications emphasize the importance of performing transcatheter PDA closure carefully and in expert hands. In our study, demographic and clinical characteristics of the patients in whom different devices were used were also analysed. It was found that PDA diameters were smaller in patients whose PDAs were closed with ADO II device rather than ADO I device. This result shows that the choice of occluder should be based on the size and anatomical features of the ductus. The device that should be preferred should be determined depending on the type, diameter and anatomical features of patient's PDA.

Study Limitations

The data was collected from a single centre, which may limit the generalizability of the results. Multi-center studies could provide more generalized outcomes. While the follow-up period averaged 5 years, longer-term follow-up would be beneficial to fully assess the sustainability of the procedure and the long-term outcomes and potential late complications.

CONCLUSION

In conclusion, our study provides important data supporting the efficacy and safety of transcatheter PDA closure in children. As a minimally invasive procedure, transcatheter PDA closure carries a lower risk of complications compared to surgical intervention and accelerates the recovery process of patients. When performed in expert hands for eligible patients, transcatheter PDA closure should be considered as the first treatment alternative in cases with PDA.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Declaration's standards and was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee (decision number: 2023/514/258/26, date: 27.09.2023).

Informed Consent: The written consent was obtained from the families of the patients included in the study.

Author Contributions

Surgical and Medical Practices: M.M.B., Concept: M.M.Y., Design: T.M., C.K., Data Collection and Processing: C.D., Y.İ.D., Analysis and Interpretation: M.M.B., G.V., Literature Search: M.M., C.D., Writing: M.M.B.

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Original Article

Evaluation of Autonomic Dysfunction in Pediatric Migraine Patients

Pediatrik Migrenli Hastalarda Otonomik Disfonksiyonun Değerlendirilmesi

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ABSTRACT

Objective: Headache during childhood is a common condition. Although recent studies have shown that the autonomic nervous system (ANS) in adult migraine patients is affected, there are few studies evaluating this relationship in children. Adult migraine patients demonstrate no abnormal ANS function in either the sympathetic or parasympathetic nervous system but there can be sympathetic/parasympathetic hypofunction/hyperfunction. The aim of this study is to investigate autonomic dysfunction in pediatric migraine patients.

Method: The study evaluated tests for autonomic functions such as the orthostatic test, 30: 15 ratio, cold-pressor test, heart-rate responses to deep and normal breathing, valsalva ratio (VR), blink reflex (BR), and sympathetic-skin-response with thirty pediatric migraine patients in interictal period. Patients in control group were selected from children that had not any other disease or headhache.

Results: Consistent with sympathetic hypofunction, there was more frequent orthostatic hypotension in migraine group (p=0.019) and negative correlation between average disease duration, migraine attack duration and orthostatic tests results. Consistent with parasympathetic hyperfunction, the migraine group had higher VRs (p=0.035). There was a negative correlation between analgesic use rate and normal respiratory-RR-interval variability and between attack rate and deep and normal-R-R interval (R-wave peak to R-wave peak in electrocardiograms) variability. There was a positive correlation between average disease duration and BR R2 and R2′ latency in migraine group (p=0.028 and p=0.027).

Conclusion: Our study revealed that ANS functions are affected in pediatric migraine and balance between sympathetic and parasympathetic nervous system is distrupted.Our study demonstrates decreased sympathetic responsiveness during the interictal period. Our results suggest hypofunction in the parasympathetic nervous system of migraine patients as attack rate and pain density elevate.

Keywords: Migraine, autonomic nervous system, blink reflex, sympathetic skin response

ÖZ

Amaç: Çocukluk çağında baş ağrısı sık karşılaşılan bir yakınmadır. Son yıllarda migrende otonom sinir sistemi fonksiyonunun etkilendiğini gösteren erişkin çalışmaları mevcut olmasına karşın çocukluk çağında bu alanda yapılmış çalışma sayısı kısıtlıdır. Bu çalışmanın amacı migrenli çocuklarda otonomik disfonksiyonun araştırılmasıdır.

Yöntem: Çalışmada otonom fonksiyonlar için baş ağrısız dönemde otuz migren hastasında "ortostatik test, 30/15 oranı, buz testi, derin ve normal solunumda elektrokardiyogramda RR (R-wave peak to R-wave peak in electrocardiograms) aralık değişkenliği, valsalva oranı, göz kırpma refleksi, sempatik deri yanıtları" değerlendirilmiştir. Kontrol grubundaki çocuklar ise baş ağrısı veya herhangi bir hastalık öyküsü olmayan sağlıklı bireylerden seçilmiştir.

Bulgular: Migren grubunda sempatik hipofonksiyonu gösterecek şekilde ortostatik hipotansiyon (p=0,019) daha sık ve ortalama hastalık süresi ile ortostatik test sonuçları arasında negatif korelasyon saptandı. Parasempatik hiperfonksiyonu destekleyecek şekilde migren grubunda valsalva oranı daha yüksek bulundu (p=0,035). Analjezik kullanım sıklığı ile normal solunum RR aralık değişkenliği arasında ve atak sıklığı ile derin ve normal solunum RR aralık analizi arasında negatif korelasyon saptandı. Ortalama hastalık süresi ile göz kırpma refleksi R2 ve R2′ latansı arasında pozitif korelasyon saptanmıştır (sırasıyla p=0,028; p=0,027).

Sonuç: Çalışmamızda pediatrik migrende otonom sinir sistemi fonksiyonlarının etkilendiği, sempatik ve parasempatik sinir sistemi arasındaki dengenin bozulduğu saptanmıştır. Çalışmamız interiktal dönemde azalmış sempatik yanıtı göstermektedir. Sonuçlarımız pediatrik migren hastalarında atak sıklığı ve ağrı yoğunluğu arttıkça parasempatik hipofonksiyonun olduğunu göstermektedir.

Anahtar kelimeler: Migren, otonom sinir sistemi, göz kırpma refleksi, sempatik deri yanıtı

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INTRODUCTION

Headache is common during childhood and patients are often referred to a neurologist. The most important and frequent cause of recurrent episodic headache is migraine. The prevalence of a headhache complaint is 37-51% in seven-year-old children and increases to 57-82% in adolescents[1]. Autonomic dysfunction can be seen in both ictal and interictal periods in patients with migraine. The pathophysiologic mechanisms of migraine are complex and yet to be fully understood. The autonomic nervous system (ANS) regulates entire unconscious homeostatic mechanism of the human body and modulate physiological pain responses including migraine. Besides the sympathetic pathways, the cranial parasympathetic system also plays a role in the migraine response[2]. Stimulation of the trigeminocervical complex of the trigeminal nucleus caudalis and spinal cord dorsal horns causes reflex activation of cranial parasympathetic fibers and chemicals such as acetylcholine, calcitonin gene related protein, vasoactive intestinal peptide are released from these particular regions[3]. Although recent studies have shown that the ANS in adult migraine patients is affected by headache, there are few studies that evaluate this relationship in children[4-9].

MATERIALS and METHODS

Thirty pediatric migraine patients who were followed in the Pediatric Neurology Department in between 2013-2015 and twenty-healthy controls were included. The study was approved by Local Ethic Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2013/18-06, date: 20.05.2013). We diagnosed the patients as migraine according to International Classification of Headache Disorders (ICHD)-II, published by the International Headache Society in 2004[10]. ICHD-III diagnostic criteria are currently used for the diagnosis of migraine. There is no difference between ICHD-II and ICHD-III in terms of migraine without aura diagnostic criteria. We included pediatric patients aged 7-18 years with migraine without aura, who did not have prophylactic treatment. They had no chronic diseases including obesity, hypertension, hyperlipidemia, thyroid function abnormalities, renal disorders, diabetes mellitus, autoimmune disorders, hepatic disorders, cardiovascular disorders, infectious disorders and neurological disorders. All the individuals had a normal neurological examination and gave consent to participate in the study. Inclusion criterias for the migraneurs are listed in Table 1. Demographic features, anthropometric measurements, localization of headache, headache attack-frequency, duration, number of emergency service admission, analgesic usage, response to analgesics, triggering factors, family history of migraine were recorded. Pediatric Migraine Disability Assessment Score (PedMIDAS) questionnaire was applied to evaluate the effects of migraine attacks on the quality of life[11]. The tests were done to evaluate autonomic functions including the orthostatic test, cold-pressor-test, blink reflex (BR), sympathetic-skin-response (SSR) tests, 30:15 ratio, heart-rate responses to deep and normal breathing and valsalva ratio (VR). All of the participants were tested in the attack free period. Electrophysiological studies were performed by the same neurophysiologist using the same electrodes in a semi-dark room with a temperature between 24-26 °C using the Keypoint EMG (Medtronic, Minneapolis, USA). During the tests, they were performed at the same time of the day (13:30-17:00) in order to prevent diurnal variation, paying attention to the absence of any external stimuli that could affect the recordings. Parents have accompanied by the cases during all tests.

Orthostatic Test

Right upper extremity blood pressure (BP) was recorded after 15 minutes of rest in the supine position, just before standing up, immediately after standing up, and one, five and ten minutes after standing up. A decrease of 20 mmHg in systolic blood pressure (SBP) and 10 mmHg in diastolic blood pressure (DBP) was accepted as orthostatic hypotension[4-6,12,13].

Cold Pressor Test (CPT)

While the patient was monitored for BP and heart rate (HR) at 24 °C room temperature, the change in HR and arterial BP was recorded during the application of cold water at a temperature of 5 °C to the dorsum of the right hand for 1 minute after 2 minutes of rest[6].

Table 1. Inclusion criterias for the migraineurs (p<0.05)
Diagnosed as migraine without aura according to ICHD-II criterias
No chronic disease or chronic medication usage
Normal physical and neurological examination
Exclusion of secondary headache causes
7-18 ages
No medication usage at least 5 days prior to admission to the study
No exposure to alcohol/nicotine at least 72 hours prior to admission to the study
SD: Standard deviation, ICHD: International Classification of Headache Disorders

Blink Reflex

Recording is performed simultaneously from both sides of the face using a two-channel recording apparatus. Surface recording electrodes are placed over the inferior orbicularis oculi muscles bilaterally. For recording the orbicularis oculi muscle, the active recording electrodes (G1) are best placed below the eye just lateral and inferior to the pupil at mid-position. The corresponding reference electrodes (G2) are placed just lateral to the lateral canthus bilaterally. The filter settings are the same as for a motor conduction study (10 Hz, 10 kHz). Once supramaximal stimulation is achieved, four to six responses are obtained on a rastered tracing and superimposed to determine the shortest response latencies. With several traces superimposed, the shortest R2-latency is selected. It is extremely important that the patient be in a relaxed state to eliminate any signal noise, which could obliterate or confound one or both components of the BR (especially R2)[14-17].

Sympathetic Skin Response

Measurement of the SSR is a non-invasive technique for assessment of sympathetic fiber impairement. SSR measurement was recorded after cleaning the skin with alcohol while the patient was lying. Surface electrode placed on the palm of the hand or sole of the foot serves best as the active electrode (E1), with the reference electrode (E2) on the dorsal surface of the same limb. In the measurement phase, basal sympathetic tone was recorded first and followed by recording SSR of the upper and lower extremities with superficial stimulation of the median nerve at the level of the left wrist. SSR latency was accepted as the starting point of negative deflection, and for amplitude, between the peaks of negative and positive deflections[18,19].

Autonomic Cardiovascular Tests

The RR (R-wave peak to R-wave peak in electrocardiograms)-Analysis, VR and 30:15 Ratio

The RR interval-test was used to examine the condition of the parasympathetic nervous system. The time between the R-peaks in the electrocardiogram (ECG) of two consecutive heart beats was measured. Measurements were recorded in rest and in deep-breathing, during valsalva-maneuver and when standing up with surface plate electrodes[5,9,13].

Normal Breathing

After the patient is advised to relax, recordings were made at rest and in supine position. Regular interval rate variation (RRIV) was calculated using the formula;

RRIV=(RR maximum-RR minimum)x100/RR mean

Deep Breathing

The patient was advised to inhale for 5 seconds, then exhale for 5 seconds. It was repeated for a few times to get a good deep respiration rhythm. When deep breathing was obtained at 6 frequencies per minute, recordings were taken in the supine position. The heart beat frequency variation is most obvious in children and young people. ECG was recorded in limb lead-II for one minute with patient breathing deeply as instructed. RRIV was calculated using the same formula with normal breathing test.

Valsalva Ratio

Patients were advised to lie down and rest for at least 10 minutes. And patients were advised to stand up when they heard the signal. ECG was recorded continuously during and after the valsalva maneuver. VR was calculated using the longest RR-interval recorded after the maneuver and the shortest RR-interval-ratio recorded during the maneuver.

Cardiovascular Response to Standing-Up and 30:15 Ratio

After 15 minutes of rest in the supine position, the RR-interval at the 15^{th} and 30^{th} heart beats of the patients who underwent ECG monitoring after standing up was recorded.

Statistical Analysis

All statistical calculations were performed using SPSS 22.0 for Windows. Whether the distributions of continuous variables were normally or not being determined by the Shapiro-Wilk test. The assumption of homogenecity of variances was examined using the Levene-test. Descriptive statistics for continuous variables were expressed as mean ± SD or median ± (25^{th}-75^{th}) percentiles, where appropriate. The Mann-Whitney U test and Student's t-test were used for the comparison of parameters. The chi-square-test was used for categorical variables. The significance level was accepted as $p<0.05$. Data analysis was performed using SPSS Statistics version-22.0 software. Mann-Whitney U test was used to compare the mean values of the groups. While the differences among categorical groups were evaluated by chi-square-test. The Pearson's correlation analysis was performed to determine the correlation between the different variables.

RESULTS

There were no statistically differences between the groups regarding age and sex (p=0.803, p=0.804).

Nineteen patients (66%) in the migraine group had a family history of migraine. No statistically significant difference was found between groups regarding body weight, height and body mass index (p=0.699, 0.172 and 0.976, respectively). Mean of SBP and DBP values were similar (p=0.639 and p=0.590, respectively). Demographic features, BP values and anthropometric measurements are given in Table 2. Number of the triggering factors including sound, light, hunger, stress, physical activity, insomnia, drug use, food intake, infection and seasonal characteristics were found as 5.7±1.0. Disease information of migraneurs are given in Table 3.

Autonomic Dysfunction Test Results

Orthostotic hypotension was detected in 10 migraneurs and one patient in the control group. This difference was statistically significant (p=0.019). There was no statistically significant difference between groups regarding other orthostotic test findings including SBP, DBP and HR during supine position, standing, one minute, 5 minute and 10 minute later standing up (Table 4).

No statisticall significant difference was found between the two groups in terms of SBP, DBP and HR before and after CPT (Table 4).

There was no statistical difference between migraine and control groups regarding latans and amplitudes which were recorded in right hand and foot of the individuals (Table 4).

No statistically signicifant difference was found between the two groups in terms of left R1, R2, R2' and right R1,R2, R2'-responses (Table 4).

No statistically difference was detected between groups in terms of 30:15 ratio and RRIV. VR was found to be higher in migraineurs than control group and the difference was statistically significant (p=0.035) (Table 4).

Table 2. Demographic features and antropometric measurements of migraneurs and healthy subjects (p<0.05)

	Migraine group (n=30)	Control group (n=20)	p-value
Age (years) (mean ± SD)	13.2±2.6	12.7±3.5	0.803
Male gender (n%)	10 (30%)	6 (%)	0.804
Systolic blood pressure (mmHg)	113.0±12.0	114.6±8.7	0.639
Diastolic blood pressure (mmHg)	68±6.9	69.3±5.6	0.590
Body weight (kg) (mean ± SD)	49.2±15.2	49.8±16.4	0.699
Height (cm) (mean ± SD)	151.9±11.1	155.4±16.4	0.172
BMI (kg/m^2) (mean ± SD)	20.7±4.7	19.9±3.7	0.976

SD: Standard deviation, BMI: Body mass index

Table 3. Disease features of migraneurs (p<0.05)

	n (%) or (mean ± SD)	min.-max.
Migraine disease duration (months)	19.3±16.2	2-60
Attack frequency	6.1±3.8	1-16
Number of attacks with a need of analgesic usage (per month)	4.6±3.3	1-12
Attack duration (hours)	6.6±7.9	1-24
Number of emergency department admissions (per year)	1.1±2.3	0-10
Complete response to analgesic	5 (16.7%)	
Partial response to analgesic	24 (80%)	
PedMIDAS score (median) Grade 1 (0-10) Grade 2 (11-30) Grade 3 (31-50) Grade 4 (>50)	12 10 (33.3%) 14 (46.7%) 3 (10%) 3 (10%)	2-96

SD: Standard deviation, PedMIDAS: Pediatric Migraine Disability Assessment Score, min.-max.: Minimum-Maximum

Table 4. Comparision of orthostotic test, cold pressure test, sympathetic skin response test, blink reflex test and 30:15 ratio, valsalva ratio and RR interval variability test results in migraine and control groups (p<0.05)				
Orthostatic test results		**Migraine group (n=30)**	**Control group (n=20)**	**p-value**
Orhostatic hypotension		10 (33.3%)	1 (5%)	0.019
Supine position	Systolic BP	115.6±12.5	116.9±8.8	0.736
	Diastolic BP	69.2±8.0	68.5±5.7	0.866
	Heart rate	87.4±13.6	88.3±12.9	0.866
After standing up	Systolic BP	111.8±14.6	107.7±11.5	0.125
	Diastolic BP	68.5±7.1	70.1±6.5	0.599
	Heart rate	96±14.8	94.6±14.9	0.789
1 minute later standing up	Systolic BP	114.0±11.3	112.5±12.4	0.706
	Diastolic BP	70.3±10.6	68.1±8.5	0.677
	Heart rate	94.6±14.3	98.0±13.7	0.326
5 minutes later standing up	Systolic BP	111.6±10.5	112.8±8.5	0.592
	Diastolic BP	71.2±7.5	68.5±6.6	0.469
	Heart rate	95.9±12.1	94.1±12.7	0.721
10 minutes later standing up	Systolic BP	109.4±12.4	110.1±9.1	0.835
	Diastolic BP	70.2±8.7	70.1±7.0	0.953
	Heart rate	94.4±10.8	94.3±12.5	0.858
Cold pressure test results				
Before cold pressure test	Systolic BP	106.0±14.7	107.0±8.5	0.764
	Diastolic BP	68.4±6.8	71.0±7.8	0.233
	Heart rate	91.2±10.3	94.2±13.8	0.412
After cold pressure test	Systolic BP	108.6±10.3	109.0±7.3	0.858
	Diastolic BP	67.9±6.7	68.7±6.2	0.696
	Heart rate	92.0±11.0	95.0±14.7	0.455
Sympathetic skin responses test results		**Migraine group (n=30)**	**Control group (n=20)**	**p-value**
Right hand	Latans (ms)	1399.8±358.45	1366.7±264.69	0.709
	Amplitude (mV)	2.65±1.56	2.29±1.39	0.406
Right foot	Latans (ms)	1795.27±380.8	1818.3±324.16	0.820
	Amplitude (mV)	1.18±0.94	0.96±0.70	0.334
Blink reflex test results				
Left R1 latans (ms)		9.89±0.64	9.91±0.82	0.940
Left R2 latans (ms)		30.92±3.31	31.27±3.93	0.750
Left R2' latans (ms)		32.73±3.78	32.6±4.32	0.960
Right R1 latans (ms)		9.63±1.72	9.85±0.97	0.574
Right R2 latans (ms)		31.80±3.44	32.48±3.35	0.491
Right R2' latans (ms)		33.62±4.38	34.51±3.73	0.443
30:15 ratio test results				
30:15 ratio		1.12±0.16	1.08±0.11	0.201
Valsalva ratio test results				
Valsalva ratio		1.63±0.36	1.46±0.35	0.035
RR interval variability in normal and deep breathing				
Normal breathing		36.5±15.6%	32.7±16.7%	0.525
Deep breathing		53.0±13.5%	54.7±10.6%	0.898
BP: Blood pressure, SD: Standard deviation, RR: R-wave peak to R-wave peak in electrocardiograms				

Table 5. Correlation analysis results RR interval variability		
	Migraine attack frequency r*	**p-value**
RRIV during normal breathing	-0.528	0.003
RRIV during deep breathing	-0.354	0.055
	Disease duration r*	**p-value**
SBP in supine position	-0.449	0.013
SBP 5 minute later standing up	-0.399	0.029
Right R2	0.402	0.028
Right R2'	0.403	0.027
	Migraine attack duration r*	**p-value**
SBP 10 minute later standing up	-0.366	0.047
DBP 10 minute later standing up	-0.397	0.030
SBP before cold pressure test	-0.512	0.004
DBP before cold pressure test	-0.380	0.038
DBP after cold pressure test	-0.394	0.031
Heart rate after cold pressure test	-0.370	0.044
	Analgesic usage r*	**p-value**
RRIV during normal breathing	-0.375	0.041
	PedMIDAS score r*	**p-value**
Heart rate before cold pressure test	-0.399	0.029
Heart rate after cold pressure test	-0.395	0.031

r*: Rate, RR: R-wave peak to R-wave peak in electrocardiograms, SBP: Sistolic blood pressure, DBP: Diastolic blood pressure, RRIV: RR interval variability, PedMIDAS: Pediatric Migraine Disability Assessment Score

Correlation Analysis

There was a negative correlation between migraine attack frequency and RRIV. A negative correlation was found between disease duration and SBP measured in supine position and 5 minutes later standing up during the orthostotic test. A positive correlation was found between disease duration and right R2 latancies of BR test. There was a negative correlation between migraine attack duration and SBP and DBP which were measured 10 minute later standing up during orthostatic test. A negative correlation was found between the duration of migraine attack and SBP, DBP measured before CPT and DBP, HR measured after the CPT. There was a negative correlation between analgesic usage and RRIV during normal breathing. A negative correlation was detected between PedMIDAS-score and HR before CPT and HR after CPT (Table 5). There was a positive correlation between average disease duration and BR-R2 and R2' latency in migraine group (p=0.028 and p=0.027; Figure 1).

DISCUSSION

Sympathetic and parasympathetic dysfunction play a significant role in migraine pathogenesis. Our study demonstrates decreased sympathetic responsiveness during the interictal period in migraneurs. Our results suggest hypofunction in the parasympathetic nervous system of migraine patients as attack rate and pain density elevate.

Sympathovagal imbalance that affects cranial vascular system that can elucidate many systemic migraine phenomena such as irritability, odor, noise, and light sensitivity, which are frequent in the prodrome period[20]. The presence of at least one cranial autonomic symptom was 27-73% in adult patients with migraine and 62% of pediatric patients[21].

Adult migraine patients demonstrate no abnormal ANS function in either the sympathetic or parasympathetic nervous system but there can be sympathetic/parasympathetic hypofunction/ hyperfunction.

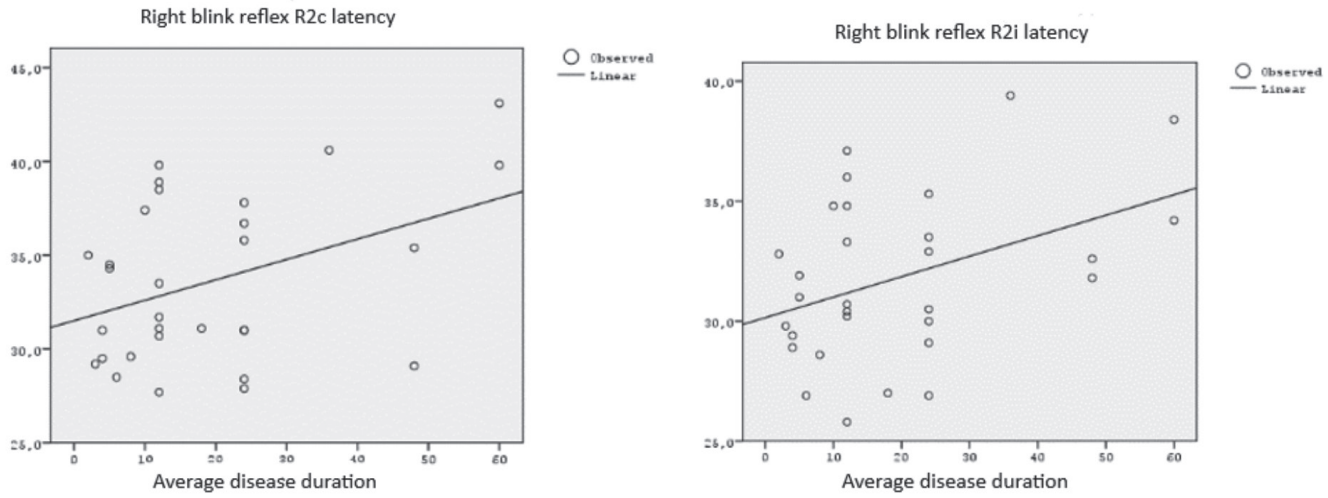

Figure 1. Positive correlation between average disease duration and blink reflex R2 and R2′ latency

In our study there were no statistically significant differences based on results of the resting BP. In the literature, some studies suggest that there is sympathetic nervous system hyperfunction in patients with migraine. Shechter et al.[22] showed that adult migraine patients had higher resting BP measured than a control group and they described this as increased sympathetic nervous system activity. Yildiz et al.[19] identified sympathetic nervous system hypofunction and hyperfunction in a re-evaluation performed 72 hours following attacks, based on SSR during attacks and the symptomatic period in adult migraine patients. Generally, most of studies demonstrate increased sympathetic nerve system activation during the ictal-period and decreased sympathetic nerve activation in interictal period in migrane group. In our study, negative correlation between SBP and DBP measured at the 10th minute during the orthostatic test and the duration of migraine attack was found. These results may show that lower SBP in patients with longer attack periods is associated with sympathetic nervous system hypoactivation. The central autonomic network (CAN) and its connections with the pain system are affected in migraine. The CAN is a system of interconnected nuclei in the cortex and brainstem that help regulate visceromotor, neuroendocrine, respiratory, and pain responses, among other functions. Important areas of the CAN that are also thought to be involved in the transmission of migraine pain include the periaqueductal gray (PAG) of the midbrain. PAG also play an important role in cardiovascular control[2]. The presence of orthostatic intolerance in migraine may be explained by this mechanism. Yakinci et al.[5] examined orthostatic test in pediatric migraine patients and showed higher systolic and diastolic BP than control group. These results suggest that sympathetic nervous system hyperactivity in migraneurs[5]. Peroutka[23] published results consistent with sympathetic nervous system hypofunction based on measurements during the asymptomatic period, in supine and upright positions, as well as evaluating plasma norepinephrine levels after the CPT. In the present study there was a negative correlation between average disease duration and SBP checked at the 5th minute and not in an upright position during the orthostatic test. Since there was a correlation with DBP, this result may linked to minimal hypoactivity in the sympathetic nervous system. In our study there was a negative correlation between SBP and DBP measured at the 10th minute during the orthostatic test and migraine attack duration. These results show that lower SBP in patients with longer attack periods may be linked to sympathetic nervous system hypoactivation. In many studies, sympathetic hypofunction was determined according to plasma norepinephrine level, cardiovascular reflex responses, and HR recovery indices, sustained handgrid tests and valsalva maneuver-phase 4[20] beat-to-beat blood pressure responses to the Valsalva maneuver, sustained handgrip, cold pressor test, and head-up tilt and tests of parasympathetic function (heart rate responses to deep breathing and the Valsalva maneuver. There was a negative correlation between average disease period and SBP and DBP measured before and after the CPT and between DBP and HR. This also shows sympathetic nervous system hypofunction since there was no HR

increase and adequate BP level after the ice-test. There was a negative correlation between PedMIDAS scores and SBP and HR before and after the ice-test. This also shows that there was no significant HR increase response to the ice-test in patients whose life quality deteriorated because of headache and that they had sympathetic nervous system hypofunction. Havanka-Kanniainen et al.[24] found lower RRIV in deep and normal breathing, which could support parasympathetic hypofunction. In the same study, the valsalva maneuver, orthostatic, and isometric exercise test had results were consistent with sympathetic nervous system hypofunction[24]. There are many studies that have also identified sympathetic nervous system hypofunction[4,19,23-28]. All of these studies show that migraine is a chronic sympathetic nervous system disease as we demonstrated in our study.

In the literature, some studies suggest that there is parasympathetic nervous system hypofunction in patients with migraine. Pogacnik et al.[12] found lower spectral-frequency dependent measurements of heart-rate-variability, which supported parasympathetic hypofunction in migraine. A study demonstrated parasympathetic hypofunction in RRIV and identified autonomous symptoms indicating ANS dysfunction[22]. Havanka-Kanniainen et al.[24] found lower RRIV in deep and normal breathing, which could support parasympathetic hypofunction. In the same study, the valsalva maneuver, orthostatic, and isometric exercise test had results were consistent with sympathetic nervous system hypofunction. These results similar to our study Mikamo et al.[28], however, established a significant difference in deep and normal breathing RRIV between migraine and control group, suggesting that parasympathetic nervous system functions were protected. Nevertheless, an orthostatic test from the same study suggested that there was sympathetic nervous system hypofunction in migraine patients, since this group had lower BP and basal plasma norepinephrine levels[28]. In the current study, there was a negative correlation between analgesic use rate and normal respiratory RRIV and between attack rate and deep and normal breathing RRIV. These results also suggest hypofunction in the parasympathetic nervous system of migraine patients as attack rate and pain density elevate.

A few studies associate migraine with parasympathetic system hyperfunction in literature. In the study conducted by Yakinci et al.[5], 25 children with migraine were evaluated during the headache-free-period and the rate of valsalva measuring parasympathetic activity was found to be higher 30:15. Gotoh et al.[29] found hyperactivity of parasympathetic nervous system based significantly on differences in Aschner's-test. In our study significantly increased valsalva-rate may suggest that parasympathetic nervous system hyperfunction in migraineurs.

There are also studies in literature demonstrating that parasympathetic nervous system functions are protected[4,7].

The BR is an objective neurophysiological method used to evaluate facial nerve and lateral medulla functions. In our study, there was no statistically significant difference between the control and migraine groups in terms of left R1, R2, R2' and right R1, R2, R2'-responses however there was a positive correlation between average disease duration and right R2, R2'-latencies of BR components. This suggests that exposure in the trigeminovascular system (TVS) increases the length of migraine periods. Normal R1-latency in BR, which is useful for evaluating trigeminovascular pathway functions, indicates that the oligosynaptic arc is protected. Longer R2, R2'-latencies show that the brain stem interneuron is suppressed and the polysynaptic pathway forming R2-response is affected. In a study conducted with migraine patients during the headache-free-period by Bánk et al.[15] R1-latency was within normal intervals in control and patient groups, but R2 and R2'-latency were statistically and significantly higher in the migraine group. They interpreted this result as indicating that the oligosynaptic pathway was protected, but there could be exposure in the trigeminal afferent and/or polysynaptic pathway[15]. In a study conducted by Yildirim et al.[17], R2-latency was higher in migraine patients and they suggested that there was a suppression of activity in brain stem interneurons.

Study Limitation

Our study has some limitations, such as the small number of patients. Recent studies have showed the ANS impairment in migraine patients. The results of ANS-tests, which are sensitive measurements, can be found very different in migraine studies. In the literature many studies, in which different methods are used to evaluate ANS, showed that patients suffering from headache have diverse physiological response to pain. The reason for the different results of the studies in the literature can be mentioned as age, gender, diversity of antopometric measurements, presence of either episodic or chronic

migraine, presence of aura, other migraine features, ictal/interictal period in each study group. Considering this situation, studies with more homogeneous study groups are needed, so we used more restrictive inclusion criteria in our study.

CONCLUSION

In conclusion, while parasympathetic hyperfunction was detected with an increased rate of valsalva in the migraine group, the presence of hypofunction in the parasympathetic system was observed as the attack frequency and headache intensity increased. The fact that orthostatic hypotension was observed more frequently in the migraine group, the insufficient cardiovascular response to the ice test, the negative correlation between the PedMIDAS-score and the ice-test, the average disease duration and the negative correlation between the parameters evaluated during the orthostatic test with the migraine attack, suggested sympathetic hypofunction in migraine. Considering the positive correlation between the average disease duration and the right R2 and R2'-latencies, which are BR components, in the correlation analysis, it can be said that the effect on the TVS increased over time during the migraine disease.

As a result, ANS functions are affected in migraine, the balance between the sympathetic and parasympathetic nervous system is disrupted, and the TVS functions are affected by the increase in the mean duration of disease in migraine.

Ethics

Ethics Committee Approval: The study was approved by Local Ethic Committee of Dokuz Eylül University Faculty of Medicine (approval number: 2013/18-06, date: 20.05.2013).

Informed Consent: All the individuals had a normal neurological examination and gave consent to participate in the study.

Author Contributions

Design: A.İ.P., İ.Ö., U.Y., A.S.H., Data Collection and Processing: D.A., N.D., Analysis and Interpretation: D.A., N.D., Literature Search: D.A., Writing: D.A.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Right Atrial Mechanics in Children with Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

Konjenital Kalp Hastalığına Sekonder Arteryel Pulmoner Hipertansiyon Olan Çocuklarda Sağ Atrium Dinamiklerinin Değerlendirilmesi

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ABSTRACT

Objective: This study aims to evaluate right atrial functions in children with pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD) by deformation indices assessed by two dimensional-speckle tracking echocardiography.

Method: A total of 40 patients, including 15 patients with World Health Organization Functional class II-III CHD-PAH and 25 age-matched healthy controls were enrolled in the study. Deformation indices were measured by electrocardiogram-gated right atrial longitudinal strain recordings.

Results: Peak atrial strain/reservoir phase (24.19±15.81 vs. 40.62±12.35%,) (p=0.01), conduit phase (15±00.13.6% vs. 26.4±10.7%) (p=0.006) and pump phase (10.06±9.07% vs. 14.21± 5.05%) (p=0.07) were comparatively evaluated in the patient and control groups, respectively Regional peak atrial strain measurements performed for basal anterolateral (p=0.06), mid anterolateral (p=0.12), apical anterolateral (p=0.61), apical inferoseptal (p=0.28) and mid inferoseptal (p=0.001), basal inferoseptal (p=0.02) segments were also compared between the patient and control groups.

Conclusion: Right atrial deformation indices were significantly impaired in patients with CHD-PAH. Deterioration in the right atrial reservoir and conduit functions are associated with right ventricular diastolic dysfunction. Both global and regional changes can be observed in the measurement of right atrial strain secondary to the existing heart defects and operative conditions of the patients.

Keywords: Pulmonary hypertension, right atrial strain, speckle tracking echocardiography

ÖZ

Amaç: Bu çalışmada konjenital kalp hastalığı (CHD) ile ilişkili pulmoner arteriyel hipertansiyonu (PAH) olan çocuklarda iki boyutlu-speckle strain ekokardiyografi ile sağ atriyum deformasyon indekslerinin değerlendirilmesi amaçlanmıştır.

Yöntem: New York Kalp Derneği fonksiyonel sınıfı II-III olan, CHD ile ilişkili pulmoner hipertansiyonlu 15 hasta ve yaşları eşleştirilmiş 25 sağlıklı kontrol olmak üzere toplam 40 hasta çalışmaya dahil edildi. Deformasyon indeksleri, elektrokardiyografi senkronize sağ atriyal strain yöntemiyle ölçülmüştür.

Bulgular: Pik atriyal strain/rezervuar fazı (hasta ve kontrol grupları, sırasıyla 24,19±15,81 vs. 40,62±12,35) (p=0,01), konduit fazı (hasta ve kontrol grupları, 15,00±13,6 vs 26,4±10,7; sırasıyla) (p=0,006) ve pompa fazı (hasta ve kontrol grupları sırasıyla 10,06±9,07 ve 14,21±5,05) (p=0,07) hasta ve kontrol grupları karşılaştırmalı olarak değerlendirildi. Altı farklı alanda bölgesel pik atriyal strain ölçümleri; bazal anterior lateral (p=0.06), medial anterior lateral (p=0.12), apikal anterior lateral (p=0.61), apikal inferior septal (p=0.28) ve medial inferior septal (p=0.001), bazal inferior septal (p=0.02) hasta ve kontrol grupları karşılaştırmalı olarak değerlendirildi.

Sonuç: Sağ atriyal deformasyon indeksleri CHD ile ilişkili pulmoner hipertansiyonlu hastalarda anlamlı olarak düşük saptandı. Sağ atriyal rezervuar ve konduit fonksiyonlarındaki bu bozulma sağ ventrikül diyastolik disfonksiyonu ile ilişkilidir. Sağ atriyum strain ölçümünde, hastaların mevcut kalp defektlerine ve ameliyat koşullarına bağlı olarak hem global hem de bölgesel değişiklikler gözlemlenebilmektedir.

Anahtar kelimeler: Pulmoner hipertansiyon, sağ atriyal strain, speckle tracking ekokardiyografi

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INTRODUCTION

Pulmonary hypertension is a progressive disease that results in hypertrophy, dilatation, and failure of the right ventricle (RV) due to increased pulmonary vascular resistance (PVR). Right atrium (RA) is also affected secondary to pulmonary hypertension. An increase in RA pressure and dilatation is reported to be a prognostic predictor for adverse outcomes[1-3]. However, data regarding right atrial reservoir, conduit, and pump functions are unsatisfactory. Two dimensional-speckle tracking echocardiography (2D-STE) is a reliable technique that allows the assessment of global and regional myocardial function as a noninvasive and quantitative approach[4,5]. After its availability, evaluation of intended cardiac cavity deformation became possible during whole cardiac cycle at one heartbeat. The method was originally used to assess left ventricular deformation, then right ventricular, left atrial, and more recently right atrial deformation[6-8]. Its usage in adult population with pulmonary hypertension, indicated that right atrial longitudinal strain decreased substantially compared to the control group and displayed an inverse correlation with RA pressure[9-11]. It has been implied in a quite limited number of studies conducted in pediatric pulmonary hypertension cases that RA functions reduced distinctly compared to the control group, suggesting that deformation indices could have a prognostic potential to predict the adverse clinical results[12].

The aim of this study was to evaluate the global and regional RA functions in patients with congenital heart disease (CHD) - pulmonary arterial hypertension (PAH) using 2D-STE. The measurements were compared with those of the control group.

MATERIALS and METHODS

Study Population

Fifteen children diagnosed with CHD-PAH were included in this study. Children in the study group have been receiving specific anti-PAH therapy (bosentan, sildenafil, iloprost, masitentan, tadalafil) and had World Health Organization functional class II or III PAH. Patients with primary pulmonary hypertension, large atrial septal defects, and left ventricular dysfunction or pulmonary vein obstruction and children that did not undergo right heart catheterization were not included in the study. Gender- and age-matched 25 healthy children were enrolled as a control group in the study. The control group included children referred to the pediatric cardiology clinic due to chest pain, tachycardia, cardiac murmur, but with cardiological examination (echocardiography and electrocardiography) results within normal range. Data related to echocardiographic parameters, results of the 6-minute walk test (6-MWT), serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels, the measurements of PVR, mean pulmonary artery pressure levels performed during cardiac catheterization were retrieved from electronic patient folders of the hospital. Informed consent was obtained from all patients and/or their parents. This prospective study and its protocol were approved by the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol no: 534, date: 11.03.2021).

Echocardiography

Echocardiographic examinations were performed using a Philips Epiq7 ultrasound machine (Philips Medical Systems, Andover, MA, USA).

Two-dimensional Speckle Tracking Analysis

Apical four-chamber views were acquired and uploaded for further analysis. The frame rate of the acquired images was generally within 40-80 Hz range. Speckle-tracking software was used to measure peak RA strain which was traced manually along the RA endocardial border. To refrain from the confounding effect of tricuspid annular motion, tracing was performed 1 mm above the atrioventricular junction. Three functional components of the RA were assessed: reservoir function (storage of blood from the systemic venous circuit during ventricular systole when the tricuspid valve is closed), conduit function (passive blood emptying into the RV when the tricuspid valve is open), pump function (contraction of the atria in late diastole to complete ventricular filling). According to the software used in this study, the RA reservoir, conduit, and pump strains were calculated with the initial reference frame set at the beginnig of the QRS-wave of the surface electrocardiogram[13]. After right atrial endocardial borders were drawn manually, RA wall was automatically split into six segments by the software program as: basal anterolateral (BAL), mid anterolateral (MAL), apical anterolateral (AAL), apical inferoseptal (AIS), mid inferoseptal (MIS), and basal inferoseptal (BIS). The global right atrial strain was automatically calculated as the averages of these six segments.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation, and nominal variables as frequencies

and/or percentages. In the comparisons of variables with normal distribution between patient and control groups t-test, and for variables with non-normal distribution Mann-Whitney U test were used.

Chi-square test was used for the comparison of categorical variables. The p-value <0.05. was accepted to be statistically significant. Inter- and intra-observer variabilities were evaluated in randomly selected 15 patients. RA strain measurements were carried out by two observers. Differences between measurements of two observers showed interobserver variability. RA measurements were repeated by an observer after four weeks. Differences between measurements performed by the same observer at baseline and four weeks later were defined as intraobserver variability. Intraclass correlation coefficient was used to in the analyses of inter- and intra-observer variabilities.

RESULTS

Demographic, clinical, and hemodynamic data are listed in Table 1. A total of 40 people were enrolled in the study, including 15 pulmonary hypertension patients with a mean age of 8.4± 6.7 years (5 female, 10 male), and 25 healthy control subjects (6 females, 19 males, average age 8.4± 4.12 years). The age and sex of the controls subjects were not significantly different from the PAH group. Thirteen of 15 patients with pulmonary hypertension had New York Heart Association (NHYA) class II, and two patients had NHYA class III PAH. Ten patients were receiving monotherapy, 5 were receiving

Table 1. Demographic, functional capacity, and right heart catheterization parameters

Demographic, functional capacity, and right heart catheterization parameters		
	Patient (n=15)	**Control (n=25)**
Age (years), [median, ([1]IQR*)]	8.4±6.77	8.4±4.12
Gender (female/male)	5F/10M	6F/19M
WHO classification	Class II: 13 Class III: 2	
Diagnoses		
[2]VSD s/p repair	4	
Unrepaired VSD	5	
Coarctation s/p repair and pulmonary banding and VSD	1	
[3]PDA (transcatheter closure) and VSD	1	
Unrepaired truncus arteriosus	1	
[4]AP Window s/p repair	1	
[5]Unrepaired DORV	1	
Tricuspid atresia	1	
Medical treatments		
Bosentan	4	
Macitentan	1	
Ilioprost	5	
Tadalafil	1	
Monotherapy	10	
Combined therapy	5	
[6]NT-pro BNP (pg/mL), [median, (IQR*)]	725 (123-12800)	
[7]6-MWT (m), [median, (IQR*)]	360 (90-520)	
[8]mPAP (mmHg), [median, (IQR*)]	63 (26-104)	
[9]PVR (Wood Units.m^2) [median, (IQR*)]	5 (2.3-45)	
PVR/SVR [median, (IQR*)]	0.4 (0.3-1.4)	

[1]IQR: Interquartile range, [1]VSD: Ventricular septal defect, [2]VSD s/p repair, VSD closed primarily with sutures or a patch, [3]PDA: Patent ductus arteriosus, [4]AP window: Aortopulmonary window, [5]DORV: double outlet right ventricle, [6]NT-pro BNP, N-terminus pro-B-type natriuretic peptide, [7]6-MWT: Six minute walk test, [8]mPAP: Mean pulmonary arterial pressure, [8]PVR: Pulmonary vascular resistance, SVR: Systemic vascular resistance

combined treatment. Five of these patients had undergone surgical interventions including VSD repair (n=3), ASD and VSD repair (n=1), aortic coarctation repair and pulmonary banding (n=1). In one case, the PDA was closed with a device using the transcatheter technique. Four patients had small-medium secundum ASD.

Peak strain values in CHD-PAH patients, right atrial reservoir function was significantly lower than the control group (24.19±15.81 vs. 40.62±12.35 respectively; p=0.001). Also right atrial passive conduit function was substantially impaired in CHD-PAH patients compared to controls (15.00±13.6 vs. 26.4±10.7, p=0.006). Although right atrial active pump function was -though not statistically significant-decreased in CHD-PAH patients relative to control subjects (10.06±9.07 vs. 14.21±5.05, p=0.07).

Regional peak atrial strain measurement values obtained from 6 different segments were lower in the study group when compared to the control group: BAL (p=0.06), MAL (p=0.12), AAL (p=0.61), AIS (p=0.28) and MIS; (p=0.001), BIS (p=0.02) (Table 2).

The intra-observer ICC coefficients for BAL (0.93), MAL (0.94), AAL (0.91), AIS (0.90), MIS (0.96), BIS (0.94) , and RA GLS (0.93) were as indicated in parentheses. The inter-observer ICCs for variability was 0.92, 0.90, 0.91, 0.93, 0.94, 0.93, 0.92 for BAL, MAL, AAL, AIS, MIS, BIS, RA GLS, respectively.

DISCUSSION

Right atrial deformation indices are promising tools to evaluate functional alterations in the mechanics of right heart in children with CHD-PAH. Previous pediatric studies had shown abnormal strain results in univentricular children[14] and patients with repaired tetralogy of Fallot[15]. Studies performed in pediatric and adult patients showed a diminished right atrial longitudinal strain in patients with PAH[10,12]. Querejeta Roca et al.[9] showed that reservoir and conduit functions of RA are reduced regardless of RA size and pressure and revealed the presence of a correlation between poor RA longitudinal strain and RV dysfunction. In our study, right atrial reservoir and conduit functions were markedly diminished in children with PAH compared with controls. Bhave et al.[15] showed that speckle strain-derived RA reservoir function may predict clinical outcome and invasive hemodynamic parameters in patients with group I PAH[16]. In another study, reservoir and conduit functions of the RA were significantly decreased although pump function was protected until the late phases of the PAH. In our study, pump phase values of PAH patients were lower than the control group without any substantial intergroup difference. In these studies mentioned above, we stated that right atrial strain values were found to be lower in the PAH group than in the control group, which is similar to our study. Nevertheless, upon comparing the studies, variations in strain values were observed both in the PAH group and the control group. This discrepancy may stem from variations in the functional capacities of the patients and differences in the methodology and software employed for the evaluation of cardiac strain. In addition, in our study, in the PAH group three patients had undergone VSD surgery, one had experienced both VSD and ASD surgery, and four patients had small - moderate

Table 2. Right atrial longitudinal and regional strain parameters

Parameters	Patient	Control	p-value
Right atrial longitudinal strain, %			
Reservoir phase, %	24.19±15.81	40.62±12.35	0.001
Conduit phase, %	15±13.60	26.4±10.70	0.006
Pump phase, %	10.06±9.07	14.21±5.05	0.07
Right atrial regional peak atrial strain			
BAL, %	47.16±3.05	77.69±33.16	0.06
MAL, %	34.13±20.08	43.84±16.71	0.12
AAL, %	16.02±22.01	18.64±10.45	0.61
AIS, %	19.97±20.50	26.74±18.03	0.28
MIS, %	25.92±13.75	47.05±19.00	0.001
BIS, %	22.60±15.34	38.99±23.09	0.02

BAL: Basal anterolateral, MAL: Mid-anterolateral, AAL: Apical anterolateral, AIS: Apical inferoseptal, MIS: Mid inferoseptal, BIS: Basal inferoseptal

ASD. Previous researches had indicated that patients undergoing surgical ASD closure exhibit a lower right atrial longitudinal peak systolic strain compared to those undergoing device closure and control subjects. Factors such as the presence of an atriotomy scar, myocardial injury, and the use of a patch may negatively impact right atrial functions[17-18]. Another study also noted a decreased right atrial longitudinal strain in individuals with ASD when compared to a healthy control group[19]. We think that these patient characteristics may also contribute to the lower strain values detected in our patients.

Atrial function plays an important role in ventricular filling as a blood storing reservoir, a conduit during early ventricular filling, and an active emptying chamber that provides additional ventricular filling with its active contraction. Recent functional and prognostic data have improved our knowledge of atrial dysfunction in cardiac mechanics before the onset of overt heart failure. As has been shown in studies investigating left atrial function, right atrial reservoir function was also identified as a prognostic parameter[20]. PAH is a progressive disease which is characterized by persistent RV pressure overload and eventual RV dysfunction. Right ventricular ability to compensate stroke volume despite increased pressure determines the survival of the patients with PAH. Lambertz et al.[20] showed that the active emptying function of the RA increased in subjects with pressure overload in the RV, which improved the diastolic filling of the RV. An experimental animal study has demonstrated an association between increased right ventricular pressure and elevated atrial active and reservoir functions, suggesting the impact of a compensatory mechanism[17].

In our study, especially MIS and BIS wall measurements in the right atrial regional longitudinal strain showed significantly lower values in the PAH group than in the control group. This is the first study to evaluate regional atrial strain among studies investigating right atrial mechanics in PAH patients. A study in which regional strain of the RA was evaluated using the 3D-STE method in operated tetralogy of Fallot patients reported that basal and mid-atrial longitudinal strain measurements in the RA were significantly lower than in the control group[21], but no comment was made on the effective etiologic factors. We think that atriotomy, patch repair of ASD, tricuspid septal leaflet takedown for VSD closure may contribute to the changes in regional atrial wall deformation.

Study Limitation

Our study was a single-center trial. Due to the small number of patients, no relationship might be established between strain analysis and clinical prognostic parameters such as proBNP and 6MWT. Echocardiographic studies and pulmonary hemodynamic measurements were not performed simultaneously. Right atrial has a thinner myocardium, which may impair signal quality, especially in the RA root. There is currently no software to be used for RA-specific speckle tracking echocardiography. In this study we used speckle-tracking software developed for LV deformation, which was reportedly used for the measurement of RA deformation in previous studies. Finally, we could not provide information about the disease course and the prognosis of the study group for a long term given the cross-sectional design of the study

CONCLUSION

Our study has revealed that the right atrial functions were substantially decreased in patients with CHD-PAH. Changes in right atrial reservoir and conduit functions are associated with right ventricular diastolic dysfunction. Both global and regional changes can be seen in the measurement of right atrial strain secondary to the existing heart defects and operative conditions of the patients.

Ethics

Ethics Committee Approval: This prospective study and its protocol were approved by the Ethics Committee of University of Health Sciences Turkey, Dr. Behçet Uz Pediatric Diseases and Surgery Training and Research Hospital (protocol no: 534, date: 11.03.2021).

Informed Consent: Informed consent was obtained from all patients and/or their parents.

Author Contributions:

Surgical and Medical Practices: G.V., T.M., M.M.Y., Concept: G.V., T.M., Design: G.V., T.M., Data Collection or Processing: G.V., T.M., E.G., C.Z., Analysis or Interpretation: G.V., M.M.Y., Literature Search: G.V., T.M., E.G., C.Z., Writing: G.V., T.M.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Evaluation of the Efficacy of Nusinersen Treatment in Patients with Late-onset SMA Using the Hammersmith Functional Motor Scale Expanded

Geç-başlangıçlı SMA Hastalarında Nusinersen Tedavisinin Etkinliğinin Genişletilmiş Hammersmith Fonksiyonel Motor Ölçeği Kullanılarak Değerlendirilmesi

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ABSTRACT

Objective: Spinal muscular atrophy (SMA) is a hereditary disorder with progressive muscle weakness and atrophy. Nusinersen is an antisense oligonucleotide directed against SMN2 and has been shown in studies to improve the motor skills of patients. The aim of this study was to evaluate the efficacy of nusinersen treatment in patients with SMA type 2 and type 3 using the Hammersmith Functional Motor Scale Expanded (HFMSE) score.

Method: The diagnosis and differentiation of SMA type 2 and type 3 were based on clinical findings and genetic tests. The HFMSE scores of all patients were evaluated in detail before nusinersen doses.

Results: Evaluation was made of a total of 15 patients, 12 SMA type 2 and 3 SMA type 3, with a median age of 13 years. None of the patients had regression of acquired abilities after nusinersen treatment. The median HFMSE score of SMA type 2 patients before treatment was 9. After nine doses of nusinersen, the HFMSE score showed a significant increase from 9 to 30 points. Although none of the patients could walk, their motor skills improved significantly. The median HFMSE score of SMA type 3 patients before treatment was 60. After 3 doses of nusinersen treatment, HFMSE scores were found to be 63.

Conclusion: Nusinersen is an effective and safe treatment for patients with late-onset SMA. It can be suggested that different motor scales should be applied and developed for SMA type 2 (sitter) and type 3 (walker) patients due to differences in the clinical characteristics of SMA types.

Keywords: Later onset SMA, nusinersen, Hammersmith Functional Motor Scale Expanded

ÖZ

Amaç: Spinal müsküler atrofi (SMA), ilerleyici kas güçsüzlüğü ve atrofiyle giden kalıtsal bir hastalıktır. Nusinersen, SMN2'ye yönelik bir antisens oligonükleotittir ve hastaların motor becerileri düzelttiği çalışmalarla kanıtlanmıştır. Bu çalışmada SMA tip 2 ve tip 3 tanısı alan hastalarda nusinersen tedavisinin etkinliğini HMFSE skoru ile değerlendirmeyi amaçladık.

Yöntem: SMA tanısı; klinik ve genetik bulgulara göre konuldu. SMA tip 2 ve tip 3 ayrımı klinik bulguların başlangıcı ve gelişim basamaklarına göre yapıldı. Tüm hastaların nusinersen dozları öncesi ve sonrası HMFCSE skorları değerlendirildi.

Bulgular: Çalışmamıza 12 SMA tip 2 ve 3 SMA tip 3 olmak üzere toplam 15 hasta dahil edildi. Hastaların ortanca yaşları 13 yaştı. Nusinersen tedavisinden sonra hiçbir hastada kazanılmış yeteneklerde gerileme olmadı. SMA tip 2 hastalarının tedavi öncesi median HFMSE skoru 9 idi. Dokuz doz nusinersen tedavisi sonrası HFMSE skorlarını anlamlı bir şekilde 9'dan 30 puana çıkardı. Hastaların hiçbiri yürüyemese de motor becerilerinde anlamlı iyileşme görüldü. SMA tip 3 hastalarının tedavi öncesi medyan HFMSE skoru 60 oldu. Üç doz nusinersen tedavisi sonrasında HFMSE skorları 63 olarak belirlendi.

Sonuç: Nusinersen geç başlangıçlı SMA hastaları için etkili ve güvenli bir tedavi yöntemidir. SMA tiplerinin klinik özelliklerindeki farklılıklar nedeniyle SMA tip 2 (oturan) ve tip 3 (yürüyen) hastalarına farklı motor ölçeklerin uygulanması ve geliştirilmesi önerilebilir.

Anahtar kelimeler: Geç başlangıçlı SMA, nusinersen, Genişletilmiş Hammersmith Fonksiyonel Motor Skalası

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INTRODUCTION

Spinal muscular atrophy (SMA) is a hereditary disorder characterized by progressive muscle weakness and atrophy caused by the degeneration of spinal anterior horn cells and loss of alpha motor neurons[1]. The incidence of SMA ranges from 4 to 10 per 100,000 live births[2-4]. In 95% of cases, the cause is a homozygous deletion of 5q13 survival motor neuron 1 (SMN1)[5]. Differences in SMN protein activity and phenotypic expression appear to be related in part to a modifier gene called SMN2[6]. A small amount (approximately 10-15%) of mRNAs from SMN2 can produce functional, full-length SMN protein[7]. Thus, the loss of SMN1 protein is partially compensated by SMN2 protein synthesis. This is a mechanism that explains some, but not all, of the phenotypic variability in patients with SMA[8]. The classification of SMA subtypes is determined by age at onset, and the clinical severity and life expectancy[9]. The natural history and examination findings in SMA depend on phenotypic variation[10]. Genetic testing is usually adequate to confirm the diagnosis of SMA. SMN2 copy number detection is usually performed simultaneously to give prognostic indication[11]. Although the main treatment in SMA is supportive care[12] modifying therapies such as nusinersen, onasemnogene abeparvovec and risdiplam have been recently developed[13]. Nusinersen is an antisense oligonucleotide directed against SMN2[14] which alters SMN2, enables pre-RNA splicing for the inclusion of exon 7, and increases the expression of functional SMN protein[14]. Nusinersen treatment for 5q-SMAs was approved by the Food and Drug Administration in December 2016[15].

The purpose of this study was to examine the changes in the Hammersmith Expanded Functional Motor Scale (HFMSE) before and after treatment in SMA type 2 and type 3 patients treated with nusinersen.

MATERIALS and METHODS

The study included SMA type 2 and type 3 patients treated with nusinersen between 2018 and 2023. Age, gender, age at onset of clinical findings, physical examination findings and genetic test results of all the patients were analyzed. The diagnosis and differentiation of SMA type 2 and type 3 was based on age at symptom onset, maximum motor skills acquired, severity of symptoms and genetic testing. In SMA type 2, symptoms appear at 6 to 18 months of age; the patient can sit but has hypotonia, areflexia, and progressive proximal weakness affecting the extremities disproportionately[9]. SMA type 3 usually occurs after the 18th month of life. Patients can walk but may need a wheelchair as the disease progresses[9,16].

The HFMSE was administered by a physiotherapist to all patients before each dose of nusinersen treatment. The HFMSE consists of 33 items investigating the child's ability to perform various activities. Each activity (item) is scored with a 2-point scoring system; 2 points for no assistance, 1 point for assistance and 0 points for incapacity. All items are tested without spinal jackets or orthoses. The total score of all the individual items ranges from a minimum score of 0 to a maximum score of 66[17].

The nusinersen injection was administered intrathecally [5 mL (12 mg) solution] by a pediatric neurologist or interventional radiologist according to the patient's degree of scoliosis. All patients were hospitalized and monitored for at least 24 hours after the application for the observation of possible side-effects. The doses were administered as four loading doses on day 0, day 14, day 28 and day 63, followed by maintenance doses every four months[18].

Ethical approval for this study was secured from the Non-Interventional Research Ethics Committee at University of Health Sciences Turkey, İzmir Tepecik Education and Research Hospital (approval number: 2023/09-68, dated: 20/11/2023). Because of the study's retrospective nature, obtaining parental consent was impossible.

Statistical Analysis

The data analysis was analyzed via Statistical Package for the Social Sciences software. The Shapiro-Wilk test was used to check for normal distribution of the data. For data that followed a normal distribution, mean and standard deviation were calculated, whereas median and interquartile range were determined for non-normally distributed data.

Categorical variables were analyzed with chi-square tests or Fisher's exact tests. To assess differences between groups for continuous variables, independent samples t-tests or Mann-Whitney U tests were applied. For comparisons involving more than two groups, analysis of variance or Kruskal-Wallis tests were used. Post-hoc analyses were conducted to pinpoint specific differences between groups. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

We evaluated 15 patients with a median age of 13 years. The median age at diagnosis was 12 months (minimum 9-maximum 18 months). The patients comprised 7 (46.7%) females and 8 (53.3%) males, as 12 (80%) who were followed up with a diagnosis of SMA type 2 and 3 (20%) with a diagnosis of SMA type 3. There was a history of consanguineous parents in 3 (20%) patients and one (6.7%) patient had a family history of SMA. The median SMN2 copy number was 3 copies (minimum 2-maximum 4). The median age at first nusinersen treatment was 8 years (minimum 1 months-maximum 15 years).

Tachycardia with respiratory distress was observed in 1 patient (diagnosed as SMA type 2) 3 days after nusinersen administration. Respiratory tract infections and cardiac causes were investigated. Pulmonary embolism was found on thoracic tomography of the patient whose respiratory distress could not be explained by other causes. Possible causes of pulmonary embolism were analyzed. No cause was found in the etiology. No side effects were observed in any other patient.

The median pretreatment HFMSE score was 60 for SMA type 3 patients and 9 for SMA type 2 patients. During the first dose, the median age was 7 years in SMA type 2 patients and 10 years in SMA type 3 patients. The median values of the HFMSE scores of SMA type 2 and type 3 before and after nusinersen treatment are summarized in Figure 1.

The median HFMSE score of SMA type 2 patients before treatment was 9. HFMSE score increased significantly after the first 4 loading doses (p=0.001). After nine doses of nusinersen, the HFMSE score showed a significant increase from 9 to 30 points. Although none of the patients could walk, their motor skills improved significantly. The median HFMSE score of SMA type 3 patients before treatment was 60. After 3 doses of nusinersen treatment, HFMSE scores were found to be 63. When the items in the HFMSE were examined in detail, it was observed that none of the patients diagnosed with SMA type 2 showed improvement in any of the movements such as standing without support, stepping, jumping forward, climbing stairs with or without handrail, and descending stairs without handrail. It was observed that all the patients diagnosed with SMA type 3 were able to perform all of these items before treatment.

Improvements in the motor skills after nusinersen are summarized in detail in Table 1.

After the nusinersen treatment, the SMA type 2 patients with an increase of ≥10 points in the HFMSE score were compared with patients with an increase of <10 points. No significant relationship was found between SMN2 copy number, age at first treatment, and HFMSE score before first treatment (Spearman's correlation 0.290, -0.315, -0.292 respectively, p>0.05).

There was no statistically significant relationship between the age at the time of initiation of the first treatment dose and the increase in the HFMSE score (p=0.243).

DISCUSSION

Although the main treatment in SMA is supportive care, recently developed disease-modifying therapies such as the promising nusinersen are now available for patients with SMA. Nusinersen is an antisense oligonucleotide directed against SMN2[19,20]. Nusinersen is one of the few treatment options that has been clinically proven effective and approved for use, and significant benefits of treatment have been shown in later onset SMA[21].

SMA type 2 patients can sit but cannot walk independently. SMA type 3 patients on the HFMSE score reach the ability to walk independently, but over time they lose motor function and many become wheelchair-dependent[1,22]. In the current study, none of the patients lost their acquired abilities after nusinersen treatment and this was similar to the findings in literature[23].

Of the items on the HFMSE, the most frequently acquired in patients with SMA type 2 were hip flexion in supine, two hands to head in sitting, rolls supine to

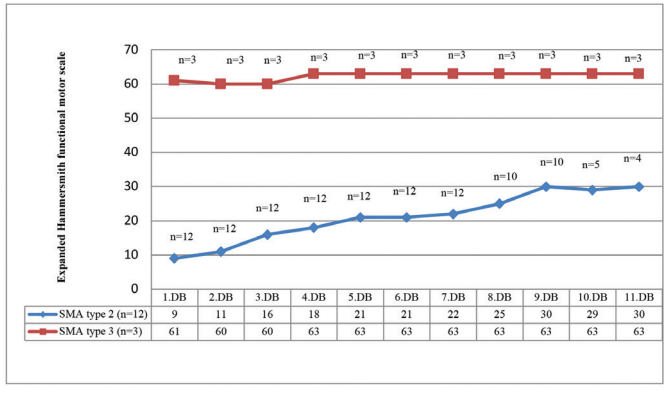

Figure 1. Hammersmith Functional Motor Scale Expanded scores before administration of each nusinersen dose (median value)

DB: Dose before, SMA: Spinal muscular atrophy

prone over, rolls prone to supine over, prop on extended arms, and long sitting, respectively.

It was observed that no patient with SMA type 2 gained ambulation ability and no improvement was found in stepping, standing unsupported, jumping forward, or ascending or descending stairs (with or without support). As far as we can see, there are no studies in the literature that have thoroughly examined the HFMSE score. However, in the study by Audic et al.[24] it was reported that none of the children could walk despite real improvements in motor function in patients with SMA type 2 who received nusinersen treatment, similar to the findings of the our study.

In this study, no significant association was found between early age at treatment initiation and increased HFMSE score, although the motor benefit is associated with early treatment as reported in other studies in the literature[25]. This was attributed to the limited number of patients involved.

Table 1. Hammersmith Functional Motor Scale Expanded items with improvement after nusinersen treatment

Item	SMA type 2 (n=12)	SMA type 3 (n=3)
1: Plinth/Chair sitting	3 (25%)	-
2: Long sitting	6 (50%)	-
3: One hand to head in sitting	5 (42%)	-
4: Two hands to head in sitting	7 (58%)	-
5: Supine to side lying	5 (42%)	-
6: Rolls prone to supine over R	5 (42%)	-
7: Rolls prone to supine over L	6 (50%)	-
8: Rolls supine to prone over R	7 (58%)	-
9: Rolls supine to prone over L	6 (50%)	-
10: Sitting to lying	7 (58%)	-
11: Props on forearms	5 (42%)	-
12: Lifts head from prone	6 (50%)	-
13: Prop on extended arms	7 (58%)	-
14: Lying to sitting	3 (25%)	1 (33%)
15: Four-point kneeling	1 (8%)	
16: Crawling	2 (16%)	
17: Lifts head from supine	3 (25%)	
18: Supported standing	2 (16%)	
19: Stand unsupported	-	
20: Stepping	-	
21: Right hip flexion in supine	9 (75%)	
22: Left hip flexion in supine	8 (83%)	
23: High kneeling to right half kneel	4 (42%)	
24: High kneeling to left half kneel	3 (25%)	
25: High kneeling to standing, leading with left leg (through right half kneel)	2 (16%)	2 (66%)
26: High kneeling to standing, leading with right leg (through left half kneel)	2 (16%)	2 (66%)
27: Standing to sitting on the floor	2 (16%)	1 (33%)
28: Squat	1 (8%)	3 (100%)
29: Jumps 12 inches forward	-	1 (33%)
30: Ascends 4 stairs with railing	-	
31: Descends 4 stairs with railing	-	
32: Ascends 4 stairs without arm support	-	
33: Descends 4 stairs without arm support	-	

In a study by Pane et al.[26], it was observed that the increase in HFMSE score in patients diagnosed with SMA type 2 became evident after the 12th month, whereas in the current study, significant improvements were observed following first 4 loading doses, in contrast to findings in literature. In SMA type 3, an increase similar to that reported in literature was observed after the 3rd dose[26].

The variability in the severity of clinical manifestations of SMA patients is partly explained by the inverse correlation with SMN2 copy number[27,28]. Nusinersen, an antisense oligonucleotide, alters SMN2 pre-RNA splicing, thereby increasing exon 7 inclusion and increasing expression of functional SMN protein[29]. The impact of SMN2 copy number on response to treatment in symptomatic patients is still unclear[30].

No significant relationship was determined between SMN2 copy number and the efficacy of nusinersen treatment in the current study, consistent with the findings of Corrati et al.[31].

Nusinersen treatment has been proven to be a safe treatment in previous studies. In the current study, with the exception of one case of pulmonary embolism of undetermined etiology, no complications were observed in the follow-up of the patients, similar to the literature[21,25].

CONCLUSION

In conclusion, nusinersen treatment is an effective and safe treatment for patients with later onset SMA. Considering the differences in the clinical characteristics of SMA types (movements that cannot be performed by patients who cannot walk or those that are expected to be performed naturally because they can walk), there can be considered to be a need for different motor scales to be developed and applied to SMA type 2 (sitter) and type 3 (walker) patients.

Ethics

Ethics Committee Approval: This study was secured from the Non-Interventional Research Ethics Committee at İzmir Tepecik Education and Research Hospital (approval number: 2023/09-68, dated: 20/11/2023).

Informed Consent: Because of the study's retrospective nature, obtaining parental consent was impossible.

Author Contributions

Concept: Y.G., P.G., N.O.D., Design: Y.G., P.G., F.B., N.O.D., Data Collection and Processing: Y.G., A.Ö.Y., B.T., Analysis and Interpretation: Y.G., Literature Search: Y.G., F.B., Writing: Y.G.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Nephrological Follow-up of Children Victims of The Earthquake: A Single Center Experience

Çocuk Deprem Mağdurlarının Nefrolojik İzlemi: Tek Merkez Deneyimi

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ABSTRACT

Objective: We retrospectively examined the nephrological conditions of the victims who applied to the Pediatric Nephrology Clinic in our hospital in İzmir after the February 6, 2023 Kahramanmaraş earthquake.

Method: Age, gender, time spent under debris, number of crushed extremities, presence of acute kidney injury (AKI), creatine kinase (CK) levels and prognosis of all patients were evaluated. 5% dextrose-0.45% NaCl solution was given as 1500 cc/m^2/day if the CK levels of the children were between 1000-3000 U/L, and as 3000 cc/m^2/day for those >3000 U/L. If the bicarbonate value is <25, alkalinization was achieved by applying $NaHCO_3$ treatment to 50 mEq/L. If CK values fell below 3000 U/L, the amount of fluid was reduced by half, and if it was below 1000 U/L, it was discontinued. If blood gas pH is >7.50 and/or bicarbonate ≥30, alkalinization treatment is discontinued; if 25-30 it is halved.

Results: Of the total 33 pediatric patients, 48.5% were girls and 51.5% were boys. The children had a mean age of 9.0±3.9 years. The mean stay under the rubble was 17.00 (4.25-48.00) hours. The CK values of 23 patients were >1000 U/L at the time of admission. Six patients had acute kidney injuries at admission. Four patients received hemodialysis and/or hemodiafiltration treatment. The CK values returned to normal in 5.0 (3.0-8.0) days in the patients who received fluid and alkalinization treatments. The serum creatinine values of all patients normalized.

Conclusion: Even in the case of concomitant AKI in crush syndrome developing after an earthquake, full recovery can be achieved with aggressive fluid and alkalinization treatment.

Keywords: Earthquake, child, crush syndrome

ÖZ

Amaç: 6 Şubat 2023 Kahramanmaraş depremi sonrası İzmir'deki hastanemizin Çocuk Nefroloji Kliniği'ne başvuran mağdurların nefrolojik durumlarını retrospektif olarak inceledik.

Yöntem: Tüm hastaların yaşı, cinsiyeti, enkaz altında geçirilen süre, ezilen ekstremite sayısı, akut böbrek hasarı varlığı, kreatinin kinaz (CK) düzeyleri ve prognozları değerlendirildi. Çocukların CK düzeyleri 1000-3000 U/L arasında ise 1500 cc/m^2/gün, >3000 U/L ise 3000 cc/m^2/gün olarak %5 dekstroz-%0,45 NaCl solüsyonu verildi. Bikarbonat değeri <25 ise 50 mEq/L olacak şekilde $NaHCO_3$ uygulanarak alkalinizasyon sağlandı. CK değerleri 3000 U/L'nin altına düşerse sıvı miktarı yarı yarıya azaltıldı, 1000 U/L'nin altına düşerse kesildi. Kan gazı pH'si >7,50 ve/veya bikarbonat ≥30 ise alkalinizasyon tedavisi kesildi; 25-30 ise yarıya düşürüldü.

Bulgular: Toplam 33 çocuk hastanın %48,5'i kız, %51,5'i erkekti. Çocukların yaş ortalaması 9,0±3,9 yıldı. Enkaz altında ortalama kalış süresi 17,00 (4,25-48,00) saatti. Başvuru sırasında 23 hastanın CK değeri 1000 U/L'nin üzerindeydi. Başvuru sırasında altı hastada akut böbrek hasarı mevcuttu. Dört hasta hemofiltrasyon ve/veya hemodiafiltrasyon tedavisi aldı. Sıvı ve alkalinizasyon tedavisi alan hastaların CK değerleri 5,0 (3,0-8,0) günde normale döndü. Tüm hastaların serum kreatinin değerleri normale döndü.

Sonuç: Deprem sonrası gelişen ezilme sendromunda akut böbrek hasarının eşlik etmesi durumunda bile agresif sıvı ve alkalinizasyon tedavisi ile tam iyileşme sağlanabilmektedir.

Anahtar kelimeler: Deprem, çocuk, ezilme sendromu

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INTRODUCTION

On February 06, 2023, an earthquake with a magnitude of 7.7 Mw on the Richter scale occurred in the southeast of Turkey, centered in Kahramanmaraş. This massive earthquake affected approximately eleven provinces and fourteen million citizens[1]. Since the earthquake occurred early in the morning, it did not give people time to escape, which increased the impactof this catastrophe.

A wide variety of factors can affect the clinical condition of earthquake victims, including the timing and severity of the earthquake, geographical, demographic factors, the architectural structure, and the seismic safety of the buildings. Mortality rates increase mainly as a result of injuries to vital organs in major natural disasters such as earthquakes, landslides, in which large numbers of people are affected at the same time, or in human-made calamities such as wars and terrorist acts[2]. The second leading cause of death in such disasters is crush syndrome (CS) resulting from blunt muscle trauma[3].

The main triggering event in the occurrence of CS is the release of components of striated muscle cells into the systemic circulation due to trauma or non-traumatic causes called rhabdomyolysis[4]. Most of the injured people pulled out of the rubble had acute kidney injury (AKI) due to rhabdomyolysis.

The most important cause of AKI is compartment syndrome, which induces hypovolemia. Since the rescued wounded do not have access to water under the wreckage, the fluid deficit is further increased by the ongoing losses. Development of AKI also depends on the severity of the muscle damage that occurs, the presence of underlying comorbid conditions, and the development of complications (e.g., sepsis). In addition, postrenal AKI due to supravesical or infravesical obstruction secondary to pelvic trauma, and AKI of renal origin due to the use of nephrotoxic agents, heart failure, arrhythmias or transfusion reaction scan also be seen[2,5].

Since the earthquake affected a very large geographical region, the injured who were removed from the rubble were first treated in the local health institutions. However, since the health institutions in the region and the health personnel working in these institutions were also affected by this disaster, some of the patients were referred to various hospitals throughout the country after their first emergency treatment. In this study, we retrospectively examined the nephrological conditions of the patients who applied to the Pediatric Nephrology Clinic of our hospital after the earthquake, which can be described as the disaster of the century.

MATERIALS and METHODS

The clinical and laboratory conditions of 33 children affected by the earthquake and followed in our clinic were retrospectively examined. Approval for the conduction of this review was obtained from the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision number: 2023/03-35, date: 05.04.2023).

Age, and gender of the patients, time remained under the rubble, cases of amputation, fasciotomy, AKI (if any), change in the amount and/or color of the voided/catheterized urine of all patients were evaluated. During the follow-up, the need for dialysis and the length of stay in the hospital were critically assessed. Systolic and diastolic blood pressures, urea, creatine (Cr), blood gas, sodium (Na), potassium (K), creatine kinase (CK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH) values of the patients were evaluated, urine tests and imaging studies were performed immediately after admission.

Those who were removed from under the rubble after the earthquake and had a CK value of >1000 U/L were diagnosed with CS[6]. AKI was diagnosed when serum creatinine levels increased more than 3 times of its cut-off values, glomerular filtration rate <75%, or urine output <0.3 mL/kg for 24 or 12 hours of anuria[7].

On the day of the earthquake, the Turkish Society of Pediatric Nephrology published practical guidelines for the management of victims to avoid development of kidney failure and disseminated this information to all hospitals that accepted or were required to admit the injured. These guidelines were related to the necessary examinations, treatment modalities and preventive measures to be implemented[8,9].

For hospitalized patients with prerenal AKI, IV fluid therapy was started at daily doses of 2000 cc/m^2. If CK levels of these children were between 1000-3000 U/L, 5% dextrose and 0.45% NaCl solution were given at daily doses of 1500 cc/m^2, if CK levels were >3000 U/L, then daily doses were increased to 3000 cc/m^2. If serum bicarbonate level was <25 mEq/L, alkalinization was achieved by applying $NaHCO_3$ treatment ata dose of 50 mEq/L. If CK values dropped below 3000 U/L in the follow-up, the amount of IV fluid replacement is halved and then stopped if CK levels fell below 1000 U/L. If blood gas pH was >7.50 and/or bicarbonate level was

≥30 mEq/L, alkalinization therapy was discontinued and halved when it is 25-30 mEq/L.

Statistical Analysis

The SPSS 26.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. Discrete variables were expressed as numbers (percentages), continuous variables with normal distribution as mean ± standard deviation, and those with non-normal distribution as median (interquartile ranges; 25-75%). Spearman Bivariate Correlations and Mann-Whitney U tests were used for statistical analysis. P-values of less than 0.05 were accepted as statistically significant.

RESULTS

Patients were firstly referred to our clinic or presented on their own on the 3rd day of the earthquake. The hospitalized children under the age of 18 (total n=33) consisted mostly of boys (51.5%) and then girls (48.5%). The children were between 2 and 16 years old, with a mean age of 9.0±3.9 years. Demographic and laboratory data of the patients are given in Table 1. The mean length of stay under the rubble (was unknown in one patient) was 17.00 (4.25-48.00) hours. Average time to rescue was significantly longer in the group with CS, at 35.5 (7.50-48.00) hours (p<0.005).

The CK values of 23 patients were >1000 U/L at the time of admission. CK values of >10,000 U/L in 3 patients before admission, returned back to normal levels at our admission. There were a total of 12 children (36.4%) with a CK level of >10,000 U/L at the time of admission. The mean CK levels were significantly higher in patients with CS at admission than in those without (p<0.05). CK values of the patients who received fluid and alkalinization therapies returned to normal within 5.0 (3.0-8.0) days.

Serum creatinine values of these patients at the time of admission ranged from 0.4 to 7.8 mg/dL, with a mean of 1.59 mg/dL. Serum creatinine values of all patients normalized in the follow-up. Five patients had AKI at admission and four patients received hemodialysis (HD) and/or hemodiafiltration (HDF) therapies. In renal ultrasonography, we did not detect any pathology

Table 1. Some remarkable demographic and laboratory data of the patients

	Crush syndrome		**p-values**
	Without	**With**	
	10 (30.3%)	**23 (69.7%)**	
Age (years)	9.5 (6.00-14.00)	8.00 (6.00-11.00)	0.576
Gender			
Male, n (%)	6 (60)	11 (47.8)	0.603
Female, n (%)	4 (40)	12 (52.2)	
Time spent under earthquake rubble (h)	4.50 (1.75-21.25)	35.5 (7.50-48.00)	0.035
CK level at admission (U/L)	145.00 (67.75-539.00)	11,838.00 (2,049.00-38,700.00)	0.00
Mean CK level (U/L)	87.02 (49.55-274.00)	3,145.50 (900.40-12,083.70)	0.00
Maximum CK level (U/L)	167.50 (67.7-539.00)	11,838.00 (2,353.00-48,860.00)	0.00
Cr level at admission (mg/dL)	0.50 (0.48-0.62)	0.50 (0.50-0.60)	0.954
Mean Cr level (mg/dL)	0.49 (0.42-0.57)	0.50 (0.40-0.57)	0.743
Maximum Cr level (mg/dL)	0.55 (0.48-0.62)	0.50 (0.50-0.70)	0.985
AST level at admission (U/L)	34.50 (24.75-65.75)	175.00 (78.00-891.00)	0.00
Mean AST level (U/L)	30.40 (24.00-41.85)	93.00 (42.20-346.60)	0.00
Maximum AST level (U/L)	53.50 (32.25-71.00)	175.00 (85.00-1.046.00)	0.00
LDH level at admission (U/L)	300.50 (223.50-453.50)	860.00 (457.00-1.991.00)	0.002
Mean LDH level (U/L)	258.60 (232.27-287.12)	449.30 (312.20-979.10)	0.002
Maximum LDH level (U/L)	375.00 (264.75-525.25)	860.00 (496.00-2.003.00)	0.001
Presence of AKI, n (%)	-	5 (21.7)	
HD/HDF, n (%)	-	4 (17.4)	
Length of hospital stay (days)	36 (16.50 - 44.75)	29.00 (17.00-47.00)	0.985

CK: Creatine kinase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, AKI: Acute kidney injury, HD/HDF: Hemodialysis/hemodiafiltration

except for one patient with a right ectopic kidney, which was not known previously. Length of hospital stay was not significantly different in patients with or without CS (p=0.985).

The correlations between the maximum serum creatinine values of the patients and the duration of their stay under the rubble, and the maximum CK, AST, LDH and K levels are shown in Table 2. We have found positively significant correlations between maximum creatinine levels and serum CK, AST and LDH levels of our patients (Table 2). The corresponding Spearman's rank correlation coefficients $(r)_s$ were 0.734, 0.598 and 0.790 and p<0.001, respectively. Serum K levels were positively but not significantly correlated with maximum creatinine values (r_s value 0.340, p=0.053).

Six patients developed AKI and underwent HD/HDF during follow-up (Table 3). Patients #16 and #31 applied with a picture of prerenal AKI, and patient #16 received IV alkalinized fluid therapy due to CS presented at admission. Patient #22 was applied with AKI and a very high CK level without any damage to the extremities, and received HDF therapy for a short period of 24 hours, together with alkaline fluid. Despite the fact that our male patient #23 who was admitted to our hospital on the 3rd day of the earthquake remained under the rubble for only 5 hours, he had not any obvious fracture, or underwent fasciotomy, etc. in his extremities, HD was performed because he had hyperkalemia that did not respond to medical treatment. In the follow-up, HDF was required for another 12 days. Our patient #24 was also admitted on the post-earthquake 3rd day. This patient who had multiple extremity injuries and, as expected, very high CK levels and AKI, received HD for 21 days. Our patient #25 was a 4-year-old patient who had a history of cardiopulmonary resuscitation after she was rescued from the wreckage and underwent HD in an external center. CS was present at admission, and creatinine values were normal when she arrived. She received HDF for 2 days. Figure 1 shows the change in kidney function test parameters during the hospitalization period of 4 patients who underwent HD/HDF.

DISCUSSION

This study aims to evaluate the nephrological status of pediatric patients followed in our clinic after the Kahramanmaraş-centered earthquake that occurred on February 6, 2023. Besides, our study conveys importance because it emphasizes that in such possible future disasters, even in the presence of AKI accompanying CS, fluid replacement therapy can reverse the situation when applied effectively.

Table 2. Correlation of maximum creatinine levels with other clinical and laboratory parameters

	Maximum creatinine level (mg/dL)	
	r	p-value
Time spent underearth quake rubble (h)	-0.154	0.399
Maximum CK level (U/L)	0.734	<0.001
Maximum AST level (U/L)	0.598	<0.001
Maximum LDH level (U/L)	0.790	<0.001
Maximum K level (mmol/L)	0.340	0.053

CK: Creatine kinase, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase, K: Potassium

Table 3. Some remarkable demographic and laboratory data of 6 patients with acute kidney injury and/or HD/HDF

Patient no	Time spent under earthquake rubble (hours)	Extremities affected (n)	Fasciotomy procedures performed (n)	Maximum CK level (U/L)	CK recovery time (days)	Maximum Cr level (mg/dL)	Cr recovery time (day)	HD /HDF	Duration of dialysis therapies (day)
16	12	2	3	62.140	8	1.5	6	-	-
22	35	0	0	98.400	12	1.37	2	HDF	1
23	5	0	0	158.980	9	7.80	32	HDF	12
24	8	4	4	284.560	10	4.40	34	HD	21
25	48	3	3	11.838	10	0.42	-	HDF	2
31	48	3	3	69	-	3.42	10	-	-

CK: Creatine kinase, Cr: Creatinine, HD/HDF: Hemodialysis/hemodiafiltration

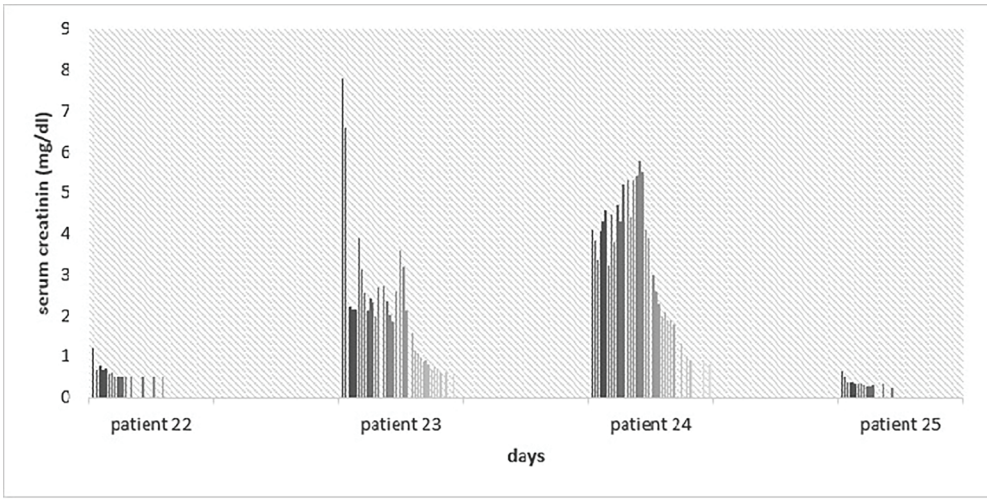

Figure 1. Serum creatinine tests during hospitalization of patient

Although there is no definitely established diagnostic criteria of CS, we accepted CK values >1000 U/L as CS in victims who were rescued from the earthquake rubble[6,10]. CS was present in 23 of a total of 33 patients. After the 1999 Marmara earthquake, Dönmez et al.[11] specified crushing injury of a large skeletal muscle mass, sensory and motor disturbances in the extremities, myoglobinuria and/or hematuria, and serum CK levels >1000 U/L as diagnostic criteria for CS in the children followed. Iskit et al.[12] reported that they accepted children with myoglobinuria or AKI (the cases with serum creatinine levels above 1.2 mg/dL or oliguria accepted as AKI) with crush injury as CS.

After crush injury, large amounts of fluid can be retained in the injured muscles, leading to compartment syndrome, hypovolemia, and ultimately AKI due to poor perfusion of the kidneys[4]. Therefore, appropriate and intensive fluid therapy should be initiated in a timely manner. Insufficient or delayed fluid administration increases the likelihood of AKI[13,14]. The prognostic factor in CS is the development of AKI, and although it is potentially preventable, it is still considered the most serious complication[15]. We also make the diagnosis of AKI when serum creatinine levels increased more than 3 times the upper limit of normal, glomerular filtration rate <75%, or urine output <0.3 mL/kg for 24 hours or 12 hours of anuria[7].

AKI was detected in 5 of our patients, and it should not be overlooked that the patients applied to us on the 3rd day at the earliest, and that some patients may have been protected from the adverse effects of AKI with fluid replacement therapy in the early period. AKI of our two patients regressed with fluid replacement therapy, while HD/HDF was applied to the other three patients. In addition, patients #16, #23 and #24 were admitted on the 3rd day after the incident of earthquake and had myoglobinuria when they were admitted, which disappeared in the first two days with fluid replacement and alkalization therapies.

Dönmez et al.[11] reported the highest CK levels in pediatric patients with CS followed up after the Marmara earthquake as 27,558 U/L in those with multiple extremity injuries. In the study of Iskit et al.[12], the development of AKI was not correlated with serum CK levels, and serum CK levels were above 10,000 U/L in only three out of 33 patients. Four of our five patients with AKI had CS and their mean CK level was 151,085 U/L. The highest CK level was found to be 284,500 U/L in our patient #24.

Oda et al.[16]; reported the incidence of AKI in children with one, two, and three extremity injuries as 50.5%, 74.5%, and 100%, respectively. In the same study, they stated that they had observed AKI in only 14.3% of children with one and 85.7% of those with multiple extremity injuries and that the number of affected extremities is an important factor in determining the severity of CS. Iskit et al.[12] reported that they could not find any relationship between the time spent under the rubble, the number of damaged extremities and the development of AKI. In our study, the mean time to stay trapped under the rubble was significantly longer in the group with CS. This is important in that it shows that the delayed rescues will expose the victims to a greater risk for CS and therefore the development of AKI.

One of the most common causes of death in injured survivors after an earthquake is cardiac arrhythmias caused by hyperkalemia. Hyperkalemia has been reported as a prominent feature of CS[17]. In their study involving 20 children, Dönmez et al.[11] stated that the increase in K levels was positively correlated with serum CK, AST, urea and creatinine levels and that CS was more severe in these children. Iskit et al.[12] detected hyperkalemia (5.6-8.2 mEq/L) in only four of the patients who developed AKI. Among the patients who applied to us, patients #23 and #24 also had hyperkalemia upon admission to the hospital. K values in other patients were within the normal range. We observed that maximum creatinine and serum CK, AST and LDH levels of our patients were positively and significantly correlated.

Isotonic sodium chloride is the preferred, and easily available electrolyte solution because it is difficult to obtain bicarbonate solutions in times of disaster[2]. The rationale for administering bicarbonate solution is that raising the urine pH above 6.5 can prevent heme-protein precipitation, intratubular plug formation, and uric acid precipitation with Tamm-Horsfall protein which will reduce the rates of metabolic acidosis and hyperkalemia. Alkalinization can also reduce the release of free iron from myoglobin and the formation of F2-isoprostane, which can increase the severity of renal vasoconstriction[18]. For this reason, we provided alkalinization with bicarbonate solutions in patients presenting with CS.

Iskit et al.[12] followed up 33 trauma patients hospitalised in the 1999 Marmara earthquake, and indicated development of AKI in 10 out of 15 cases with crush injuries. They reported that 4 of these patients received IV infusion of 0.33% or 0.45% NaCl solution at daily doses of 6000 mL/m^2 or at least 3000 mL/m^2 and despite these aggressive fluid resuscitations, two of them needed HD[12]. They stated that since AKI is seen only in children with crush injuries, this type of injury is the main cause of AKI in pediatric patients who are trapped under earthquake rubble. Dönmez et al.[11] reported that they did not detect AKI in any of the eight pediatric patients in whom fluid resuscitation was initiated in the rescue area after the Marmara earthquake, and that AKI occurred in seven (58%) of 12 children who had not started to receive fluid therapy in the early period. They reported that even though they administered fluid replacement therapy at an average daily dose of 2500-3000 mL/m^2, four children needed treatment with HD[11]. Sanadgol et al.[19] stated that in the Iran-Bam earthquake, none of the pediatric patients could be started on fluid therapy in the rescue area because the earthquake was severe and all the medical facilities in the region were damaged. They stated that they had given alkaline solution (15 mEq/L bicarbonate/isotonic sodium chloride) in cases where serum CK levels were 3-5 times the upper limit of normal, serum K values were above 5.5 mEq/L, and in the concomitant presence of myoglobinuria. They reported that AKI had not developed in any patient without crush injury, but it had occurred in 8 (53%) of 15 patients with crush injury, but none of these patients had required dialysis. Here, too, since AKI had been observed only in their patients with crush injuries, they also emphasized that crush injury was the main cause of AKI in these patients. They concluded that the amount of fluid that should be administered to prevent the development of AKI in children with crush injuries should be greater than 4.8 times the amount of the maintenance fluid[19]. There is no clear data on the amount, content and alkalinization amount of the fluid to be given to children presenting with CS. First of all, we used 5% dextrose and 0.45% NaCl solution because of its easy accessibility. We adjusted the bicarbonate dose to be administered according to the blood bicarbonate level. With the aggressive fluid therapy and alkalinization we applied, all patients who developed CS recovered within a short time.

The extent of the damages caused by the earthquakes is associated with many factors such as earthquake resistance of the buildings, the condition of the water supplies, and weather conditions in the region. For example, the Marmara earthquake occurred during the summer months when the air temperature was higher. It should not be overlooked that fluid loss in victims also contributes to AKI. The study conducted by Bakkaloğlu et al.[20] presented the most comprehensive nationwide post-earthquake kidney disaster data in pediatric victims.

The strength of our study is the detailed description of fluid therapy in the presence of limited literature on children victims of the earthquake.

Study Limitations

Scarce number of patients included in our study, our inability to measure height of the patients, and calculate their eGFRs accordingly due to the fact that almost all of the children had lower extremity damage were limitations of our study. In addition, since the first medical interventions of the patients were performed in an external center. we could not reach the previous impressions of some patients due to communication problems in the first days of the earthquake.

CONCLUSION

CS-induced AKI resolves in the long term without any damage to the kidneys. It should be noted that even when dialysis is not possible in cases with post-earthquake CS, these patients should never be left untreated, because the effects of CS can be prevented by aggressive fluid and alkalization therapies.

Ethics

Ethics Committee Approval: Approval for the conduction of this review was obtained from the Ethics Committee of University of Health Sciences Turkey, İzmir Tepecik Training and Research Hospital (decision number: 2023/03-35, date: 05.04.2023).

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: C.B., Ö.Ö.Ş., D.A., S.A.Ç., F.M., A.B.A., B.K.D., Concept: C.B., Ö.Ö.Ş., D.A., S.A.Ç., F.M., A.B.A., B.K.D., Design: C.B., Ö.Ö.Ş., D.A., S.A.Ç., F.M., A.B.A., B.K.D., Data Collection and Processing: C.B., Ö.Ö.Ş., D.A., S.A.Ç., F.M., A.B.A., B.K.D., Analysis and Interpretation: C.B., D.A., S.A.Ç., F.M., A.B.A., B.K.D., Literature Search: C.B., B.K.D., Writing: C.B., B.K.D.

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Original Article

Is Idiopathic Cuneate Gyrus Herniation an Isolated Variant or a Coexisting Finding in Pediatric Cases? An Magnetic Resonance Imaging Based Study

Pediatrik Hastalarda İdiyopatik Kuneat Girus Herniasyonu Tesadüfi mi Yoksa Eşlik Eden Bir Bulgu mu? Manyetik Rezonans Görüntüleme Temelli Çalışma

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ABSTRACT

Objective: We aimed to investigate whether idiopathic cuneate gyrus herniation (ICH) is an anomaly or a normal variant, its prevalence, whether there is a coexisting finding or pathology, as well as to characterize it with magnetic resonance imaging (MRI) findings.

Method: We evaluated 0-17-year-olds' brain MR images from January 2021-August 2023 at our clinic. Standard brain protocols utilize 1.5 Tesla MRI scanners. ICH and congenital brain abnormalities were evaluated in optimal brain MRIs. Malformations were classified as posterior fossa anomalies (PFA), commissural and cortical developmental anomalies (CCDA), and midline malformations.

Results: Our study comprised 691 pediatric brain MRIs with a mean age of 5.93±3.4 years, with 48.77% male and 51.23% female. The mean age of 32 ICH (+) patients was 6.19±4.02 years, with 40.63% male and 59.37% female. The prevalence of ICH was 32/691 (4.6%). In 63 (9.11%) congenital brain malformation patients, ICH presence differed (p=0.005). Congenital brain malformation patients with ICH showed a significantly higher PFA rate (n=8) than without ICH. The frequency of CCDA (n=23) and the association of PFA and CCDA (n=12) were significantly higher in ICH patients with congenital brain malformation. The frequency of congenital brain malformation was higher in 32 ICH (+) patients, with a rate of 50% (p<0.001).

Conclusion: We found that ICH is more frequent than reported and may be associated with congenital brain malformations. ICH must be differentiated from pathology to avoid unnecessary procedures. Congenital brain abnormalities may accompany ICH and should be carefully screened.

Keywords: Brain herniation, cuneate gyrus, idiopathic, malformation

ÖZ

Amaç: İdiyopatik kuneat girus herniasyonunun (IKH) anomali veya normal bir varyant mı olduğunu, prevalansını, eşlik eden ek bulgu ya da patoloji varlığını araştırmayı ve manyetik rezonans görüntüleme (MRG) bulguları ile tanımlamayı amaçladık.

Yöntem: Kliniğimizde Ocak 2021-Ağustos 2023 arasında çekilmiş 0-17 yaş aralığında pediatrik beyin MR görüntüleri retrospektif tarandı. Tetkikler 1.5 Tesla MRG tarayıcı ile standart beyin protokolü uygulanarak gerçekleştirilmiştir. Optimal görüntü kalitesine sahip olguların beyin MRG'leri IKH ve konjenital beyin malformasyonu varlığı yönünden değerlendirildi. Malformasyon saptanan olgular posterior fossa anomalisi (PFA), komissural ve kortikal gelişim anomalileri (KKGA), orta hat malformasyonları olarak gruplandırıldı.

Bulgular: Çalışma kapsamına alınan 691 olguda ortalama yaş 5,93±3,4 idi. %48,77'i erkek, %51,23'ü kadındı. IKH (+) 32 olgunun yaş ortalaması 6,19±4,02 olup %40,63'ü erkek, %59,37'i kadındı. IKH prevelansı 32/691 (%4,6) idi. Altmış üç (%9,11) olguda konjenital beyin malformasyonu saptanmış olup IKH (+) ve IKH (-) grupta anlamlı farklılık gösterdi (p=0,005). Konjenital beyin malformasyonlu IKH (+) olgularda PFA olan bireylerin (n=8) frekansı IKH (-) gruptan anlamlı yüksekti. Konjenital beyin malformasyonlu bireylerde IKH (-) olanlarda KKGA (n=23) ve PFA ile KKGA birlikteliği (n=12) olanların frekansı anlamlı yüksekti. IKH (+) olan 32 olguda konjenital beyin malformasyonu görülme oranı %50 ile oldukça yüksekti (p<0,001).

Sonuç: Çalışmamızda IKH'nin literatürde belirtilenden daha yüksek bir prevelansa sahip olduğunu ve konjenital beyin malformasyonlarında eşlikçi olabildiğini gösterdik. IKH'nin tanınması patolojilerden ayırt etmede ve gereksiz işlemleri önlemede önemlidir. Olgular IKH'ye eşlik edebilecek konjenital beyin malformasyonları yönünden de dikkatlice taranmalıdır.

Anahtar kelimeler: Beyin herniasyonu, kuneat girus, idiyopatik, malformasyon

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INTRODUCTION

Brain herniation is a serious neuropathology that refers to the displacement of brain tissue from one location to another. Acute and chronic pathologies such as trauma, brain tumors, intracranial hemorrhages, cerebral edema, hydrocephalus, and infections are among the causes of acquired brain herniations[1,2]. Idiopathic brain herniation (IBH) is the abnormal displacement of brain tissue towards adjacent anatomical structures, without a known cause. It is rarely described in the literature[3] and has been reported to develop in the cuneate gyrus, precuneal gyrus, parahippocampal gyrus, lateral temporal lobe, and inferior temporal gyrus[3-6].

The cuneus is located medial to the occipital lobe, between the calcarine sulcus and the lingual gyrus, and just anterior to the precuneus on the medial aspect of the parietal lobe. It is formed by the differentiation of the dorsal part of the neural tube and is shaped by specific developmental patterns, gene expression, and morphogenetic movements during the early developmental stages of the brain[7,8]. Located in both cerebral hemispheres, the cuneus has important roles in cognitive and visual processes: it is located in the primary and secondary visual cortex and plays a critical role in the processing of visual information. It is especially activated in response to visual stimuli and is closely connected to the primary visual cortex[8].

"Idiopathic cuneate gyrus herniation (ICH)" indicates that the herniation occurs without a known cause. There is no reliable information on the actual prevalence or incidence of ICH, and as of the time of this report, only thirteen cases have been reported in the literature[3,9,10]. The etiology is unclear, but in idiopathic cases, there may be abnormalities at the time of brain development. Some of the cases described in the literature appear wholly coincidental, whereas some have clinical symptoms, such as headaches. In the literature, in a case with parahippocampal idiopathic brain herniation, this benign condition was mistakenly biopsied for a mass[10]. For these reasons, it should be noted that ICH may in fact be a normal finding: there may be accompanying anomalies or cranial pathologies, and it is important to differentiate these from the masses in order to prevent unnecessary interventions. The etiopathogenesis of congenital brain malformations is diverse and complex, with some of these being genetically based and some others sporadic and in addition, the components of malformations grouped under one heading are usually more than one.

Based on clinical experience, we hypothesized that ICH and congenital brain malformations may coexist. Therefore, in this study, we aimed to investigate whether ICH is an anomaly or a normal variant, what is its prevalence in childhood, whether there is an accompanying finding or pathology in the cases, and to define it with magnetic resonance imaging (MRI) findings.

MATERIALS and METHODS

Study Design and Population

Our study was planned as a single-center retrospective analysis. Pediatric brain MR images obtained in our clinic between January 2021 and August 2023 were retrospectively evaluated. A pediatric radiologist and a radiologist with more than five years of experience in pediatric neuroradiology, performed the MRI evaluations by consensus. The medical records of all patients were analyzed using the hospital automation system. The MRI evaluations were made using the INFINITT picture archiving and communication system [PACS 3.0.11.4 (BN11)] (INFINITT Healthcare Co., Seoul, Korea) software.

Patients aged 0 to 17 years with optimal brain MRI images were included in the study. Those showing pathologies that may cause acquired herniation (trauma, ischemia, infection, neoplasia history, diagnosed or follow-up neurological disease) were excluded, as well as those patients with poor image quality and technical artifacts in brain MRI images. The study was conducted in accordance with the Helsinki Declaration's standards and was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee (decision number: 2023/514/258/26, date: 27.09.2023).

MRI Technique and Analysis

MR imaging was performed with a 1.5 Tesla (T) MRI scanner (Philips Ingenia, The Netherlands). Axial spin echo T1W (TR/TE= 470-570/12-30 ms), axial and sagittal T2W (TR/TE= 4500-6000/90-110 ms), axial and coronal FLAIR (TR/TE= 6000-9000/100-120 ms), and diffusion weighted imaging (DWI) (b=0, 500, 1000) sequences were used to obtain structural images of the whole brain for anatomical reference. All sequences were obtained with 5 mm slices. To assess the presence of ICH, any displacement of the bilateral cuneate gyri in the occipital lobe towards the superior cerebellar cisterns medially, was visually observed (Figures 1, 2). The findings detected on T1A and T2A axial images were confirmed on sagittal images, unilateral or bilateral presence was also evaluated (Figure 3). All MRI images were also evaluated

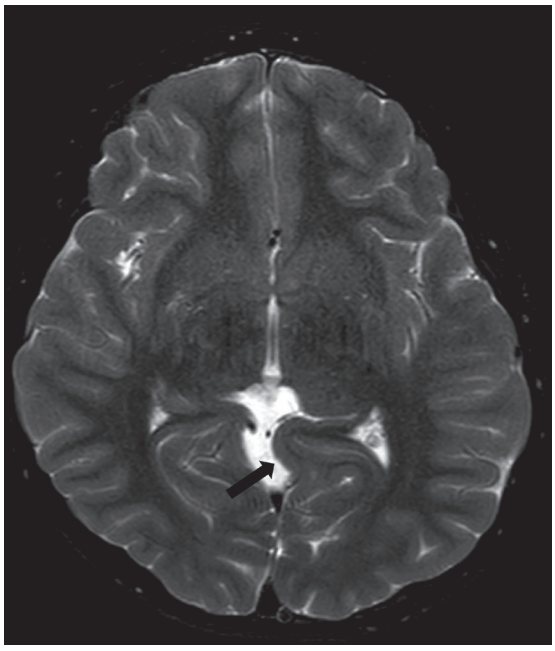

Figure 1. Axial T2-weighted brain MR image shows unilateral cuneate gyrus herniation on the left (black arrow)

MR: Magnetic resonance

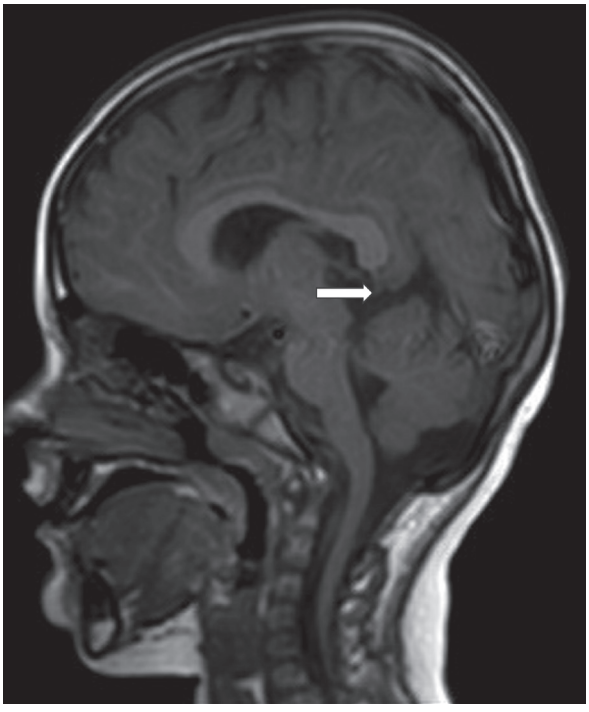

Figure 2. In the sagittal T1-weighted MR image of the same patient as Figure 1, the herniated cuneuate gyrus extends towards the superior cerebellar cistern (white arrow)

MR: Magnetic resonance

for neurologic pathologies, other common variations, and congenital brain anomalies.

A morphologic-based approach was used to classify congenital malformations in MRI scans[11]. Accordingly, malformations were divided into posterior fossa malformations, commissural and cortical developmental anomalies (CCDA), as well as midline malformations. Posterior fossa malformations included Chiari malformations and hindbrain malformations (Dandy Walker spectrum and various other malformations). Cortical and commissural developmental anomalies were further divided into commissural anomalies (callosal dysgenesis spectrum) and cortical developmental malformations. Cortical developmental malformations were further subdivided into those secondary to glial/neuronal proliferation or apoptosis, malformations secondary to neuronal migration abnormalities, and postmigrational developmental disorders.

Statistical Analysis

The relationship between congenital anomalies and ICH was statistically evaluated. The SPSS version 22.0 was used for statistical analysis, and complementary statistical methods were used to evaluate the data (mean, standard deviation, median, frequency, percentage,

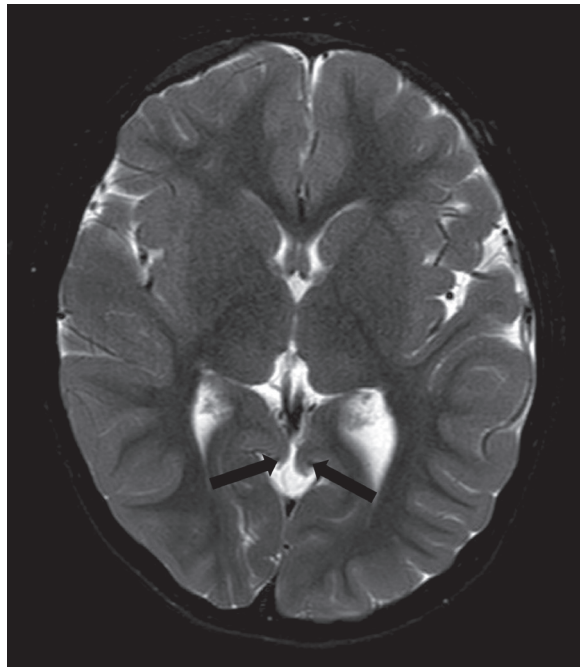

Figure 3. In another case, axial T2-weighted MR image shows bilateral cuneate gyrus herniation (black arrows)

MR: Magnetic resonance

minimum, and maximum). Fisher's exact test was used to evaluate the relationship between congenital brain malformations and the presence of ICH; Fisher-Freeman-Halton exact test was used to evaluate the relationship between subgroups of congenital brain malformations and the presence of ICH. A p-value <0.05 was considered statistically significant.

RESULTS

In the study, 738 brain MRI examinations were analyzed according to the inclusion and exclusion criteria. In line with these, twelve cases were excluded due to a diagnosed neurologic disease (cerebral palsy, periventricular leukomalacia, multiple sclerosis), eight cases due to brain mass, six cases due to meningitis, nine cases due to acute or sequelae trauma findings, and twelve cases due to poor image quality. Some 691 brain MRI scans included in the study were evaluated for the presence of ICH, variations, and anomalies (Figure 4). The mean age of these patients was 5.93±3.4 years. There were 337 (48.77%) males and 354 (51.23%) females. The number of ICH (+) cases was 32 (4.6%) and 659 cases were ICH (-).

The mean age of ICH (+) cases was 6.19±4.02 years. The gender distribution of ICH (+) cases was 13 (40.63%) males and 19 (59.37%) females. Among ICH (+) cases, right ICH was seen in 10, left ICH in 5, and bilateral ICH in 17 cases. The prevalence of ICH was 32/691 (4.6%) in our population, and in all ICH (+) cases, the herniated cuneate gyrus was located toward the superior cerebellar cistern. MRI signal characteristics of the herniated parenchyma were normal in all ICH (+) cases.

In those that were ICH (-), the mean age and gender distribution were 5.72±3.21 years and 341 (52.75%) males and 318 (48.25%) females, respectively.

Congenital brain malformations were detected in 63 (9.11%) of the 691 screened cases. Among these patients, 16 (25.4%) were ICH (+) and 47 (74.6%) were ICH (-). The incidence of congenital malformations was statistically significantly higher in ICH (+) patients than in ICH (-) patients (50% vs. 7.1%) (p<0.001) (Table 1).

The distribution of the presence of ICH among the subgroups of patients with congenital brain malformations is shown in Table 2. Accordingly, in 16 ICH (+) patients, eight had posterior fossa anomalies (PFA), five had anomalies of commissural and cortical development, two had midline malformations and one had a combination of midline malformation, and posterior fossa anomaly. None of the eight patients with posterior fossa malformations had Chiari malformation. Of these patients, two had pontocerebellar hypoplasia, one had cerebellar hypoplasia, one had a cerebellar hypoplasia + arachnoid cyst, one had cerebellar dysplasia, two had mega cisterna magna, and one had vermis hypoplasia. No compression sign or secondary

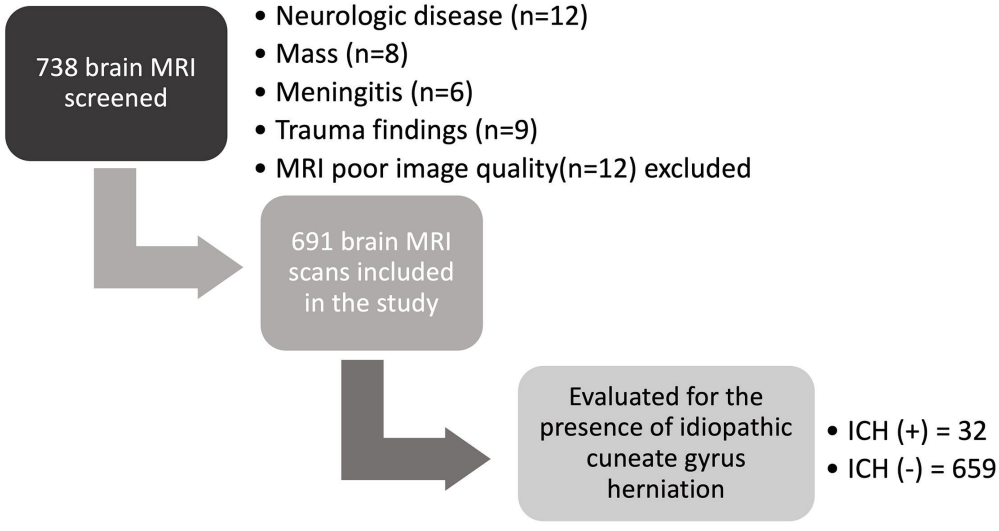

Figure 4. The determination of our study population according to the inclusion and exclusion criteria and the summary of our study findings are presented in the diagram

MRI: Magnetic resonance imaging, ICH: Idiopathic cuneate gyrus herniation

herniation was detected due to the existing pathologies. Of the 47 ICH (-) patients, 11 had PFA, 23 had CCDA, 12 had an association of PFA with CCDA, and one had a midline malformation. There was a statistically significant difference in terms of anomalies between ICH (+) and ICH (-) patients with congenital brain malformations (p=0.005). This variance is due to the difference in the rates of PFA and posterior fossa+ CCDA in ICH (+) and ICH (-) patients. In patients with congenital brain malformations, the frequency of patients with PFA (n=8) in the ICH (+) group was significantly higher than in the ICH (-) group (p=0.005). In addition, the frequency of commissural anomalies (n=23) and posterior fossa+ CCDA (n=12), is significantly higher in the ICH (-) group with congenital brain malformations (p=0.005). Among all cases evaluated in our study, there were only two Dandy-Walker malformations, and these were ICH (-). In these cases, there was no evidence of obstructive hydrocephalus or a large volume or tumoural herniation requiring a cystoperitoneal shunt.

DISCUSSION

In this study, we investigated for the first time the prevalence of ICH by MRI in childhood and the presence of coexisting congenital malformations; thus, our findings are unique and introductory. We found that ICH has a higher prevalence than reported in the literature, and we demonstrated the coexistence of ICH in congenital brain malformations.

Table 1. Distribution in terms of presence of ICH in patients with congenital brain malformations

CBM		ICH (+)	ICH (-)	Total
CBM (+)	Count, %	16 (25.4%)	47 (74.6%)	63 (100.0%)
	% within ICH	50	7.1	9.1
	% of total	2.3	6.8	9.1
CBM (-)	Count, %	16 (2.5%)	612 (97.5%)	628 (100%)
	% within ICH	50	92.9	90.9
	% of total	2.3	88.6	90.9
Total	Count, %	32 (4.6%)	659 (95.4%)	691 (100.0%)

CBM: Congenital brain malformation, ICH: Idiopathic cuneate gyrus herniation

Table 2. Distribution among subgroups of patients with congenital brain malformations in terms of the presence of ICH

CBM		ICH (+)	ICH (-)	Total CBM
Posterior fossa anomalies	Count	8_a (42.1%)	11_b (57.9%)	19 (100%)
	% in ICH	50.0	23.4	30.2
	% total	12.7	17.5	30.2
Comissural-cortical developmental anomalies	Count	5_a (17.9%)	23_a (82.1%)	28 (100%)
	% in ICH	31.3	48.9	44.4
	% total	7.9	36.5	44.4
Posterior fossa anomalies + comissural-cortical developmental anomalies	Count	0_a (0.0%)	12_b (100.0%)	12 (100.0%)
	% in ICH	0	25.5	19
	% total		19	19
Midline malformation	Count	2_a (66.7%)	1_a (33.3%)	3
	% in ICH	12.5	2.1	4.8
	% total	3.2	1.6	4.8
Midline malformation + posterior fossa anomalies	Count	1_a (100.0%)	0_a (0.0%)	1 (100.0%)
	% in ICH	6.3	0.0	1.6
	% total	1.6	0.0	1.6
Total CBM	Count, %	16 (25.4%)	47 (74.6%)	63 (100.0%)

Each subscript letter donates a subset of each categories whose column proportions do not differ significantly from each other at the 0,05 level
CBM: Congenital brain malformation, ICH: Idiopathic cuneate gyrus herniation

ICH is an abnormal displacement of brain tissue from the cuneus region to the adjacent anatomical structure, without a known cause. In order to detect the presence of ICH, this condition should be recognised, and the relevant anatomical region should be carefully evaluated on a brain MRI. When ICH, which is an unusual condition, is detected, pathologic conditions such as mass and edema should be differentiated initially. As the etiology of ICH has not been fully elucidated, abnormalities during embryologic development may be considered[10]. To our knowledge, thirteen ICH (+) cases have been reported in the literature, eleven of which were reported by Maldjian and Adam[9] in a comprehensive computed tomography (CT) prevalence study. As a case report, only one adult case was reported by Duarte et al.[10] and a pediatric case reported by Koc et al.[3] is also available. Another case of idiopathic brain herniation reported in the literature was misinterpreted as a mass on an MRI and a biopsy showed normal brain tissue[12]. In this report, a 41-year-old man was admitted to the hospital with right-sided atypical trigeminal neuralgia, and radiological imaging revealed an abnormal left ambient cistern, which was interpreted as a mesial temporal lobe or extramedullary ambient cistern mass lesion. Surgical exploration for biopsy revealed an abnormal anatomy of the posterior fossa and parahippocampal herniation into the perimesencephalic cistern, which was confirmed to be normal brain tissue by biopsy and defined as idiopathic brain herniation. This case shows us the importance of radiological and clinical recognition of ICH, which is a benign condition among idiopathic brain herniations. Unlike ICH, acquired brain herniations require treatment of the causative pathologic condition, and the approach depends on the cause of the herniation, its severity, and the patient's general health status and symptoms. Treatment may include emergency or elective surgery or other medical interventions.

There is only one prevalence study for ICH in the literature, performed by Maldjian and Adams[9]. In this CT-based study, the prevalence of ICH was reported as 0.73%[9]. In our MRI-based study, we found a prevalence of 4.6%. The CT prevalence study was performed in patients presenting to the emergency department and since the age of the study population was not specified, we believe it includes the entire adult as well as the paediatric population. The higher soft tissue resolution of MR compared to CT does have an impact on the numerical difference between our study and the CT study, but this alone did not explain the discrepancy. We also believe that the fact that our study was performed in a paediatric population, including not only emergency but also outpatient-urgent patient groups, and was performed in a tertiary care center, is also noteworthy. We suspect that the detection rate will increase along with the awareness of "idiopathic brain hernias", which we believe is not fully known by both clinicians and radiologists. In addition, the fact that the rate is higher in the paediatric population compared to the general population suggests the possibility that ICH may become involutional over time, or that those with accompanying severe malformations may not reach advanced ages. However, prospective long-term studies including larger case series are required to substantiate this assumption.

In the multicenter population-based EUROCAT study of the epidemiology of congenital brain malformations in Europe, 4,927 cases with congenital cerebral anomalies were identified, with a prevalence (adjusted for under-reporting) of 9.8 [95% confidence interval (CI): 8.5 to 11.2] per 10,000 births. Forty-eight percent of all cases were reported as an isolated cerebral anomaly. It was emphasized that the incidence varied considerably between regions and according to the regularity of record-keeping. The study also reported that the prevalence increased by 2.4% per year (95% CI: 1.3% to 3.5%), excluding genetic or chromosomal conditions, with increases occurring only for congenital formations of the corpus callosum (3.0% per year) and 'other reduction deformities of the brain' (2.8% per year)[13]. In our study, the rate of congenital brain malformations was relatively high, at 9.11%, however the majority of our patients with congenital brain malformations had callosal anomalies with 28.57% (n=18) and posterior fossa malformations with 52.38% (n=33). In our ICH (+) patients, malformations were seen in 50% of the cases, and 50% of these were posterior fossa malformations. The high rate of accompanying congenital brain malformations in our ICH (+) patients suggested that ICH may not be an isolated variant, but rather a finding that is associated with congenital brain malformations that may be caused by an abnormality during embryonic developmental stages. ICH (+) cases should be carefully evaluated for these possible malformations. In the literature, it has been reported that this anomaly may be due to a defect in the meningeal embryogenesis stage. During early development, the meningeal layer separating the telencephalon and diencephalon regresses as differentiation progresses, and the thalamic tissue becomes contiguous with the base of the cerebrum. As embryonic development progresses, the median part of the tentorium becomes invaginated, and only the lateral parts remain. As theorized in the Chiari type II malformation, the local influence of the factors

regulating this development on the tentorial dura may cause a dural defect, leading to small focal herniation of the parenchyma[10,14-16]. In this context, prospective MRI-based studies including thin-section contrast-enhanced sequences in large case groups, may be useful to evaluate the dural defect.

In acquired brain herniations, headaches, nausea, vomiting, altered consciousness, and neurologic deficits often occur clinically, due to increased cerebral pressure. Specific symptoms may be observed depending on the localization. In IBH cases in the literature, headache was described as a clinical finding in some cases, and trigeminal neuralgia was reported as an additional finding in another case. Aside from these, no significant additional pathology, variation, or anomaly was described in the cases. However, the posterior part of the cuneate gyrus has projections from the fovea, and the anterior portion has projections from the peripheral visual field. Sequelae may occur due to the abnormally positioned area, or the patient may adapt his or her vision by using the other visual field, and progress with normal vision throughout his or her life[9,10]. Visual evoked fields or functional MRI may be helpful to demonstrate this, however no such study is available in the literature. In our study, headache was defined in five of the ICH (+) cases. No congenital brain malformation was found in any of these cases, and there was no specific clinical symptom in the other cases in our study.

We endeavoured to evaluate the relationship between ICH and congenital malformations, which are hypothesised to start in the intrauterine period. We know that paediatric brain tumours are caused by disorders in developmentally regulated signalling pathways, but tumours are evaluated under a separate heading from malformations. Among paediatric brain tumours, congenital brain tumours are the most likely to cause primary herniation, however congenital brain tumours are extremely rare. Other brain tumours that are more common in paediatric age may cause secondary herniation, such as cerebellar tonsil, uncal, and subfalcin herniations. Secondary herniation sites that can be caused by both congenital and acquired tumours are anatomically distant from ICH, however we are unable to determine whether a congenital tumour in the occipital lobe can cause ICH. This can be considered as a limitation, and it should be the subject of another study.

Study Limitations

Our study had some other limitations. Firstly, it has a retrospective design, and we could not establish a standardized imaging protocol. Although our sample was large, the number of samples in our variation and anomaly subgroups was small. Another limitation is that it was conducted in a pediatric population: for a prevalence study, a more comprehensive survey, including the adult population, may be useful. Finally, our retrospective study design did not allow us to perform an additional evaluation of cuneal region function in our patients. We identified headache as a clinical finding in the retrospective file searches of our patients, however we could not obtain information about visual symptomatology.

CONCLUSION

In conclusion, our childhood-based study showed that the prevalence of ICH is higher than reported in the literature. Congenital malformations accompanying ICH in our cases may be coincidental or may be one of the signs of an effect in the early stages of embryonic development. Therefore, knowledge of ICH is necessary to differentiate it from pathology and to prevent unnecessary procedures. In addition, knowing that ICH may be accompanied by congenital malformations is important in terms of careful screening of brain tissue for congenital malformations in ICH cases.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Declaration's standards and was approved by University of Health Sciences Turkey, Kartal Dr. Lütfi Kırdar City Hospital's Ethics Committee (decision number: 2023/514/258/26, date: 27.09.2023).

Informed Consent: Retrospective study.

Author Contributions

Concept: E.C., Design: H.G.D., E.C., Data Collection and Processing: H.G.D., E.C., Analysis and Interpretation: H.G.D., E.C., Literature Search: H.G.D., E.C., Writing: H.G.D.

Conflict of Interest: The authors have no conflict of interest to declare.

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Original Article

Esmolol Infusion in Pediatric Intensive Care; 2 Years Retrospective Review

Çocuk Yoğun Bakımda Esmolol İnfüzyonları; 2 Yıllık Retrospektif İnceleme

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ABSTRACT

Objective: Esmolol is an exceptionally effective cardio-selective β (1)-receptor blocking agent that demonstrates a swift onset and a brief duration of action. Our goal in this research was to delve into the utilization of esmolol, a potent intravenous beta blocker agent, among pediatric patients in the intensive care unit who possess various medical conditions.

Method: Our research conducted over a span of two years between December 2020 and 2022, took place at the pediatric intensive care unit (PICU). The demographics, primary diagnoses, intensive care admission diagnoses, blood pressure levels, indications for starting esmolol, echocardiographic imaging findings of patients using esmolol infusion, esmolol doses, duration of use, reason for discontinuation, need for mechanical ventilation, use of inotropes, and pediatric risk of mortality score IV scores of patients using esmolol infusion were recorded in the data set.

Results: The lowest starting dose of esmolol infusion (n=37) was determined as 25 mcg/kg/min and the highest dose as 250 mcg/kg/min. The median age of the deceased patients was significantly high. Additionally, the esmolol infusion doses of the surviving patients were higher. In the surviving patients, the median esmolol dose was found to be significantly higher, while the median age was significantly lower.

Conclusion: The use of esmolol through intravenous infusion in PICUs requires careful consideration and monitoring of the patient's hemodynamic and clinical parameters. Our experience has shown that esmolol can effectively regulate heart rate at low dosages.

Keywords: Esmolol, pediatric intensive care, tachycardia

ÖZ

Amaç: Esmolol, hızlı bir başlangıç ve kısa bir etki süresi ile etkili bir kardiyo-selektif β (1)-reseptör bloke edici ajandır. Bu araştırmadaki amacımız, güçlü bir intravenöz beta bloker ajan olan esmololün çeşitli tıbbi rahatsızlıkları olan yoğun bakım ünitesindeki pediatrik hastalarda kullanımını araştırmaktı.

Yöntem: Aralık 2020 ile 2022 yılları arasında iki yıllık bir sürede yürütülen araştırmamız çocuk yoğun bakım ünitesinde (ÇYBÜ) gerçekleştirildi. Esmolol infüzyonu kullanan hastaların demografik özellikleri, temel tanıları, yoğun bakıma yatış tanıları, kan basıncı düzeyleri, esmolol başlama endikasyonları, ekokardiyografik görüntüleme bulguları, esmolol dozları, kullanım süreleri, bırakma nedenleri, mekanik ventilasyon ihtiyacı, inotrop kullanımı ve esmolol infüzyonu kullanan hastaların pediatric risk of mortality score IV skorları veri setine kaydedildi.

Bulgular: Esmolol infüzyonunun en düşük başlangıç dozu (n=37) 25 mcg/kg/dk, en yüksek dozu ise 250 mcg/kg/dk olarak belirlendi. Ölen hastaların ortanca yaşı anlamlı derecede yüksekti. Ayrıca hayatta kalan hastaların esmolol infüzyon dozları daha yüksekti. Hayatta kalan hastalarda ortanca esmolol dozu anlamlı derecede yüksek, ortanca yaş ise anlamlı derecede düşük bulundu.

Sonuç: ÇYBÜ'lerde intravenöz infüzyon yoluyla esmolol kullanımı, hastanın hemodinamik ve klinik parametrelerinin dikkatli bir şekilde değerlendirilmesini ve izlenmesini gerektirir. Deneyimlerimiz esmololün düşük dozlarda kalp atış hızını etkili bir şekilde düzenleyebildiğini göstermiştir.

Anahtar kelimeler: Esmolol, çocuk yoğun bakım, taşikardi

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INTRODUCTION

In pediatric intensive care units (PICUs), monitoring the vital signs of patients is an essential component of the treatment process, particularly when it is conducted in conjunction with a multisystem examination. This is especially true for patients who are at risk for complications related to their cardiac function, which can be adversely affected by primary cardiac diseases

or secondary involvement in other medical conditions. Arrhythmias are a common concern in cases of primary cardiac disease, as they can have serious consequences for the patient's overall health. However, the need for treatment methods that aim to correct the patient's hemodynamics may also arise in cases where the patient is experiencing clinical conditions that could negatively impact their cardiac function, such as septic shock caused by severe infections. Therefore, it is imperative that the vital signs and cardiac function of these patients are carefully monitored and monitored in order to ensure that appropriate treatment is provided in a timely manner.

Esmolol is an exceptionally effective cardio-selective β1-receptor blocking agent that demonstrates a swift onset and a brief duration of action[1]. Despite the potential for an increased risk of hypotension, its effect can be swiftly reversed. Its elimination half-life is shorter in newborns and infants compared to children of the pediatric age group (>2 years). Esmolol has been demonstrated to be highly effective in controlling abnormal and elevated hemodynamic parameters in patients suffering from supraventricular tachyarrhythmia, hypertension, and tachycardia, with a noticeable reduction in these conditions seen in conjunction with its use. Infusions of esmolol have also been shown to be beneficial in the acute treatment of cardiac arrhythmias and hypertension in children[2]. In recent years, it has also been utilized in the termination of supraventricular arrhythmias in postoperative cardiac patients for the control of hypertension following cardiac surgery, as well as in the regulation of tachycardia and hyperdynamic profile in cases of sepsis and septic shock[3].

Our goal in this research was to delve into the utilization of esmolol, a potent intravenous beta blocker agent, among pediatric patients in the intensive care unit who possess various medical conditions. By scrutinizing the literature from a pediatric standpoint, we discovered that esmolol has been studied for its pharmacokinetic and therapeutic effects, as well as its use post-cardiac surgery[4,5]. However, we sought to share our own observations and experiences with esmolol in a general pediatric intensive care setting, where patients may present with a range of diagnoses. Thus, we conducted a retrospective analysis on the indications, methods of use, and outcomes of esmolol infusions in the patients we monitored.

MATERIALS and METHODS

Our research project, conducted over a span of two years between December 2020 and December 2022, took place at the PICU. The study involved the examination of the medical records of the patients who were hospitalized during this period, with a focus on the use of intravenous esmolol. All of the relevant clinical notes and treatment orders were carefully reviewed and analyzed in order to gain a comprehensive understanding of the effectiveness of these medications in the treatment of the hospitalized patients. Overall, our research aims to provide valuable insights and recommendations for the use of esmolol in pediatric intensive care settings.

The demographic data, primary diagnoses, intensive care admission diagnoses, blood pressure levels, indications for starting esmolol, echocardiographic imaging findings (if any) of patients using esmolol infusion, esmolol doses (with the highest dose used for each patient noted), duration of use, reason for discontinuation, need for mechanical ventilation, use of inotropes, and pediatric risk of mortality score IV scores of patients using esmolol infusion were recorded in the data set. Each inotrope was grouped separately. Echocardiography results were recorded but patients with multiple findings were not grouped and were not included in statistical analysis due to the presence of multiple findings.

Statistical Analysis

The statistical analysis of the data was performed by the SPSS software (version 22.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics of categorical and numerical data were performed. The distribution of numerical data was evaluated using the Shapiro-Wilk test, histogram, and plot graphics. Non-parametric tests were used due to the non-normal distribution and the median interquartile range values were given.

The study was approved by the Ethics Committee of Health Sciences University of Turkey Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital (protocol no: 813, date: 09.02.2023) and written informed consent was obtained from the parents of all participating subjects.

RESULTS

In our study, the data of 37 patients were analyzed. Demographic data and patient characteristics of these patients are given in Table 1. The lowest starting dose of esmolol infusion was determined as 25 mcg/kg/min and the highest dose as 250 mcg/kg/min. Upon starting esmolol, it was determined that cardiology consultation was requested for 32 (86%) of the total 37 patients and

Table 1. Demographic data, diagnosis, PRISM IV score and esmolol variables of patients using esmolol	
Demographics	**n=37**
Gender	**n (%)**
Male/female	23 (62.2)/14 (37.8)
Age	**Median; (IQR)**
Months	41; (116)
Primary diagnosis of patients	**n (%)**
Norological disease	8 (21.6)
Hematological disease	7 (18.9)
Cardiovascular disease	5 (13.5)
Nephrological disease	4 (10.8)
Metabolic disease	7 (18.9)
Immunological disease	2 (5.4)
Gastroenterological disease	2 (5.4)
Without chronic disease	2 (5.4)
PICU admission diagnoses	**n (%)**
Hypertension	1 (2.7)
Respiratory failure	8 (21.6)
Cardiac failure	2 (5.4)
Septic shock	16 (43.2)
Metabolic crisis	1 (2.7)
MIS-C	1 (2.7)
Acute renal failure	1 (2.7)
Post-CPR	5 (13.5)
Change of consciousness	2 (5.4)
Blood pressures	**Median; (IQR)**
Systolic blood pressure	90 (15)
Diastolic blood pressure	55 (11)
Mean arteriel pressure	69 (13)
Indications	**n (%)**
Hypertension	3 (8.1)
Sinus tachycardia	25 (67.6)
Supraventrcular tachycardia	8 (21.6)
Ventricular tachycardia	1 (2.7)
Esmolol	**Median; (IQR)**
Maximum dosage (mcg/kg/min)	50 (37.5)
Infusion time (hour)	17 (63)
Reason for discontinuation	**Median; (IQR)**
Bradycardia	1 (2.7)
Normocardia	17 (45.9)
Normotension	5 (13.5)
Atrial flutter	1 (2.7)
Medication change	3 (8.1)
Hypotension	2 (5.4)
Exitus (during medication)	8 (21.6)
Mortality scores	**Median; (IQR)**
PRISM IV	9 (11.5)
PRISM IV (%)	4.62 (17.11)

PRISM IV: Pediatric risk of mortality score IV, MIS-C: Multisystem inflammatory syndrome in children, CPR: Cardiopulmonary resuscitation, IQR: Interquartile range, PICU: Pediatric intensive care unit

echocardiographic evaluation was performed. In the echocardiographic imaging of these patients, it was seen that 8 (25%) of them had normal findings. In the other patients (75%), findings such as valve insufficiencies and stenoses, operated or non-operated congenital heart defects, pericardial effusion, pulmonary hypertension, and hypertrophic cardiomyopathy were detected.

The relationship between esmolol dose, duration of use, heart rate and ejection fraction, and inotropic use, and mechanical ventilation is given in (Table 2.) The number of patients using dobutamine and milrinon was too small for statistical analysis. The relationship between the presence of mortality and esmolol dose, duration of use, age, and blood pressure values was investigated. The median age of the deceased patients was significantly high. Additionally, the esmolol infusion doses of the surviving patients were higher (Table 3).

All of the exitus cases were accompanied by underlying chronic diseases, while 7 of them were being followed with a diagnosis of septic shock and 1 with a diagnosis of septic shock and acute respiratory distress syndrome. Two cases were receiving esmolol due to supraventricular tachycardia, while the others were receiving it due to sinus tachycardia. In the surviving patients, the median esmolol dose was found to be significantly higher, while the median age was significantly lower. The reasons for ceasing esmolol were evaluated according to the use of noradrenaline or adrenaline. The median values for esmolol use were significantly higher and age median values were significantly lower in surviving patients (Table 4).

DISCUSSION

Our PICU serves as a center of medical expertise where we treat a wide range of critical illnesses, excluding trauma cases. Given the delicate nature of critical patients, we often must implement cardiac support therapies to address any issues that may arise and impact hemodynamics. We use most frequently employed methods for this purpose include inotropic treatments, fluid therapy, and treatments targeted towards arrhythmias in our intensive care unit. Our studies have shown that the patients admitted to our intensive care unit frequently suffer from chronic diseases, with neurological, metabolic, and hematological ailments being among the most prominent.

Sympathetic-induced tachycardia typically occurs in septic shock patients to compensate for severe

Table 2. Analysis of esmolol, heart rate and ejection fraction variables according to inotrope types and mechanical ventilation use

Treatment variables n (%)	Esmolol dosage (mcg/kg/min) median (IQR)	Esmolol ınfusion time (hour) median (IQR)	Heart rate median (IQR)	Ejection fraction (%) median (IQR)
Inotrop				
Used =29 (78.4)	50 (25)	17 (63)	180 (30)	61 (18)
Unused =8 (21.6)	50 (68.75)	26.5 (60)	167.5 (33)	74 (6.25)
	p=0.506	p=0.897	p=0.281	**p=0.028**
Adrenalin				
Used =17 (45.9)	50 (37.5)	17 (64)	167.5 (28)	63 (20)
Unused =20 (54.1)	50 (43.75)	24 (63)	188 (23)	64 (14)
	p=0.722	p=0.692	p=0.08	p=0.618
Noradrenalin				
Used =26 (70.3)	50 (25)	19.5 (65)	179 (30)	63 (16)
Unused =11 (29.7)	50 (75)	17 (41)	170 (30)	69 (21)
	p=0.738	p=0.441	p=0.618	p=0.75
Dopamin				
Used =10 (27)	37.5 (31.25)	52 (186)	169 (38)	62 (17)
Unused =27 (73)	50 (50)	16 (41)	175 (30)	64 (19.5)
	p=0.502	p=0.028	p=0.692	p=0.768
Dobutamin				
Used =3 (8.1)	25 (25-50)	12 (4-32)	220 (150-230)	54 (50-58)
Unused =34 (91.9)	50 (50)	19.5 (65)	172.5 (30)	65 (19)
	N/A	**N/A**	**N/A**	**N/A**
Milrinon				
Used =2 (5.4)	62.5 (25-100)	18.5 (6-31)	190 (180-200)	65 (16.75)
Unused =35 (94.6)	50 (25)	17 (65)	170 (30)	46 (37-55)
	N/A	**N/A**	**N/A**	**N/A**
Mechanical ventilation				
Used =30 (81.8)	50 (25)	27 (60)	176.5 (30)	62.5 (19)
Unused =7 (18.9)	50 (75)	5 (28)	170 (40)	67 (17.5)
	p=0.314	p=0.111	p=0.891	p=0.876

IQR: Interquartile range, N/A: Not applicable

Table 3. Esmolol dosage, infusion time, age and blood pressure with mortality

Mortality	Age (months) median (IQR)	Esmolol dosage median (IQR)	Infusion time median (IQR)	Heart rate median (IQR)	Systolic blood pressure median (IQR)	Diastolic blood pressure median (IQR)	Mean arterial pressure median (IQR)
Survival	28 (43)	50 (50)	31 (67)	170 (30)	90 (16)	55 (10)	69.97 (11)
Exitus	181 (86)	25 (18.75)	15.5 (25)	176.5 (35)	90 (19)	55 (23)	66.67 (21)
p-value*	**0.001**	**0.044**	0.196	0.867	0.615	0.866	0.81

*Mann-Whitney U test, IQR: Interquartile range

Table 4. Analysis of the reasons for discontinuation of esmolol according to the use of noradrenaline or adrenaline				
Reason of discontinuation	**Noradrenalin n=26 (70.3) n (%)**		**Adrenalin n=17 (45.9) n (%)**	
	Used	**Unused**	**Used**	**Unused**
Bradycardia	0	1 (9.1)	0	1 (5)
Normocardia	12 (46.2)	5 (45.5)	10 (58.8)	7 (35)
Hypotension	2 (7.7)	0	0	2 (10)
Normotension	3 (11.5)	2 (182)	1 (5.9)	4 (20)
Atrial flutter	0	1 (9.1)	0	1 (5)
Medication change	1 (3.8)	2 (18.2)	0	3 (15)
Exitus	8 (30.8)	0	6 (35.3)	2 (10)

hypotension, hypoperfusion, and low cardiac output. Despite successful resuscitation with fluids and vasopressors, according to current clinical guidelines, this high heart rate is often persistent in these patients and usually results from long-term adrenergic stimulation of the heart. This uncontrolled tachycardia has been independently associated with increased mortality risk, so it can be harmful to the patient's condition if not treated properly. Persistent tachycardia is often seen in septic shock patients undergoing resuscitation and is an independent risk factor for increased mortality[6,7]. Almost half of the cases in which we applied esmolol treatment were in septic shock. We saw that the drug was started most often due to sinus tachycardia, which is a result of sympathetic system activation in the septic shock cases. In recent studies on adult cases, the effects of esmolol infusion on heart rate control and clinical outcomes in septic shock patients with tachycardia and hyperdynamic hemodynamic profile have been examined and it has been reported that it can reduce heart rate and increase survival rate. It has also been reported that there is no increase in the adverse effect of esmolol infusion on average arterial pressure[8,9].

In our cases, the median value of blood pressures was within the normal range. Monitoring patients under inotropic treatment and the doses of esmolol infusion may explain this situation. Since our study was a retrospective research, it was not classified as an adverse event, but the reasons for discontinuing the drug could be examined from this perspective. We had cases that developed bradycardia, hypotension and atrial flutter. Hypotension may have developed due to the progression of the shock syndrome in the patient. The case with bradycardia had diastolic dysfunction and pulmonary hypertension along with valve insufficiencies in the echocardiography evaluation. Due to his hypertensive values, esmolol infusion was started and he was not currently receiving inotropic treatment. In the other case where the reason for discontinuation was identified as atrial flutter, we think that we cannot provide definite information about the specific side effect of esmolol infusion in this critical patient due to the multiple medications being taken.

In our study, it was seen that there was no difference in esmolol dose (mcg/kg/min), infusion time, and heart peak values depending on the use of inotropes. At least 1 inotrope was used in 78% of cases. We think that the very small number of patients in our study who did not receive inotropes may affect this result. No difference was also detected when the use of different inotropes was categorized. Dynamic titration of inotropic doses according to the clinic and vital signs of the patient may have affected these values. In a study of cardiac surgery cases, it was shown that esmolol infusion was associated with a decrease in inotropic score in the postoperative period[10]. In our study, the relationship between esmolol infusion and inotropic score was not examined because this should have been prospectively recorded but our study was retrospective. The ejection fractions determined by echocardiography in patients who started inotropes were found to be significantly low. This is an expected situation that can be explained by the need for inotropes in these patients.

It was observed that cases where exitus occurred while receiving esmolol infusion were lost due to acute multiple organ failure related to the underlying illness. This was not due to a complication related to esmolol. Additionally, the low maximum doses of esmolol in these patients suggests that there was not sufficient hemodynamic stability for titration to higher doses of esmolol. Efforts to correct hemodynamic findings in septic shock may not always have a positive outcome. In a randomized controlled study of 1122 adult patients, it

was reported that esmolol did not reduce the need for vasopressors or improve the return of shock in patients with septic shock[11].

We saw that in most of the patients (81.1%), a cardiology consultation was requested and an echocardiographic evaluation was performed. We strongly recommend a cardiology evaluation for the detection of primary heart pathologies and secondary cardiac involvement in critically ill children and intensive care patients. Before starting esmolol infusion, the ejection fraction, contractile functions, and valve functions of the heart can be evaluated. The compensatory mechanisms that occur to ensure sufficient blood circulation in the body should be considered[12]. We recommend closely monitoring blood gas lactate levels and capillary filling times to see the adequacy of tissue circulation in patients receiving esmolol. In addition, in our cases, we saw that electrocardiogram evaluation with cardiac enzyme levels normal in cases where echocardiography was not seen prior to esmolol infusion. These cases were all evaluated as sinus tachycardia.

We frequently detected the reason for discontinuation of infusions in patients using esmolol as normotension and normocardia. It can be said that sympathetic system activation was controlled in these cases. Titration and effectiveness of inotropes may also have contributed to this process. In terms of case numbers, we only analyzed the reasons for discontinuation separately in noradrenaline and adrenaline infusions. The number of patients receiving other inotropic treatments was not sufficient for analysis. In critically ill children, sedation and analgesia play an important role in the success of treatment in intensive care. Inadequate sedation/analgesia should definitely be considered as one of the causes of tachycardia[13]. We have identified that sedation/analgesia has been initiated in all of our cases. In our clinic, we frequently use benzodiazepines and opioid derivative agents. The sedoanalgesic agents used are dynamically titrated according to patient need, so we could not access them from retrospectively recorded notes.

Study Limitation

Limitations of our study include being retrospective, having a small number of patients, being unable to determine the presence of different interventional procedures during tachycardic episodes, and being unable to evaluate the detailed trends of heart rate in detail.

CONCLUSION

In summary, the use of esmolol through intravenous infusion in PICUs requires careful consideration and monitoring of the patient's hemodynamic and clinical parameters. Our experience has shown that esmolol can effectively regulate heart rate at low dosages. Further research, in the form of prospective, randomized controlled studies, is necessary to evaluate the effects of esmolol in combination with various inotropic agents, sedative medications, and inotropic scores in critically ill pediatric patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Health Sciences University of Turkey Dr. Behçet Uz Children's Diseases and Surgery Training and Research Hospital (protocol no: 813, date: 09.02.2023).

Informed Consent: Written informed consent was obtained from the parents of all participating subjects.

Author Contributions

Surgical and Medical Practices: P.H., Concept G.A., Design: G.A., P.H., U.K., Data Collection or Processing: A.G., Ö.S.S., Analysis or Interpretation: G.A., F.S., G.C., Literature Search: G.A., Ö.S.S., P.H., Writing: G.A., G.C., H.A.

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Letter to the Editor

Kawasaki Disease in a 4-Year-Old Male Child with Brucellosis

Brusellozlu 4 Yaşında Erkek Çocukta Kawasaki Hastalığı

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Dear Editor,

Kawasaki disease (KD) is an acute vasculitis of childhood that leads to the development of coronary artery aneurysms in untreated cases. It is the leading cause of acquired heart disease in children in developed countries. Although various infectious agents, including bacteria, viruses, and superantigens, have been proposed as potential triggers for KD, its etiology is still unknown[(1)]. Here, we present a patient who had the diagnostic criteria of KD during concomitant Brucella infection.

A 4-year-old boy was admitted to our hospital with malaise and persistent fever, which had started 15 days prior. During this period, he developed an erythematous macular rash, eye redness, and red cracked lips. He had been treated with antibiotics and paracetamol before admission, but his fever and fatigue persisted. Upon readmission, he presented with swelling in his hands and feet. Some remarkable laboratory test results were as indicated: leukocyte: 14,040/mm³, neutrophil: 9,330/mm³, lymphocyte: 2,940/mm³, platelets: 853,000/mm³, hemoglobin: 11.2 g/dL, C-reactive protein: 1.9 mg/dL, erythrocyte sedimentation rate: 57 mm/h. While levels of transaminases, albumin, sodium, and urinary analytes were within their normal limits. He was evaluated by echocardiography and no coronary artery aneurysm, valvular regurgitation, and pericardial effusion was observed. Based on these findings, he was diagnosed with KD. The patient was promptly treated with intravenous immunoglobulin at the dosage of 2 g/kg for one day plus acetylsalicylic acid at the daily doses of 90 mg/kg for 3 days which was continued at daily doses of 5 mg/kg.

It was learned from his medical history that he consumed unpasteurized dairy products and brucellosis was endemic in the region. Therefore, immunohistochemical tests to reveal (if any) Rose Bengal, immunoglobulin G and -Brucella immunoglobulin M (IgM) antibodies were conducted. Both Rose Bengal and Brucella IgM-positivities were detected indicating a concurrent Brucella infection. The patient received rifampicin and sulfamethoxazole-trimethoprim combination for 6 weeks. He recovered completely

during follow-up based on the evaluation of clinical and laboratory parameters.

While rare, concurrent bacterial and viral infections with KD have been reported in the literature[2,3]. A single-center retrospective study indicated that the presence of infection does not alter the clinical phenotype or coronary outcomes of KD[3]. There has been at least one reported case of brucellosis occurring alongside KD similar to our case[2]. Brucellosis, caused by Gram-negative bacteria of the genus Brucella, is a zoonotic infection transmitted to humans primarily through contact with infected animals or consumption of contaminated food products. It typically presents with nonspecific symptoms such as fever, malaise, and arthralgia, and requires appropriate antibiotherapy[4].

This case emphasizes that in areas where brucellosis is endemic, clinicians should be aware that KD and brucellosis may occur concurrently.

Ethics

Informed Consent: Retrospective study.

Author Contributions

Surgical and Medical Practices: E.K., A.D., Concept: E.K., A.D., Design: E.K., Data Collection and Processing: E.K., A.D., Analysis and Interpretation: E.K., Literature Search: E.K., Writing: E.K.

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