Original Article

COMPARISON OF THE EFFECT OF SILDENAFIL AND TADALAFIL ON PULMONARY HYPERTENSION ASSOCIATED WITH HEMODYNAMICALLY SIGNIFICANT PDAS TREATMENT OF PULMONARY HYPERTENSION IN HS-PDA PATIENTS

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Abstract

Objective: Treating the hemodynamically significant patent ductus arteriosus (hs-PDA) includes conservative therapy besides using non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen. In addition, the pulmonary arterial pressure increases in hs-PDA. It is not clear whether the drugs used in acute pulmonary arterial hypertension (PAH) can improve the hs-PDA or not. This study evaluates the effect of anti-PAH drugs, sildenafil and tadalafil on patients with hs-PDA and PAH.

Methods: Neonates with hs-PDA and PAH diagnosis are included in this triple-blinded clinical randomized trial study. The patients are assigned to group A (tadalafil + acetaminophen), B (sildenafil + acetaminophen), and C (acetaminophen alone). The patients were evaluated by their echocardiography findings, before and after therapy.

Results: Overall, 96 patients were included in this study, 32 for each group. The patients were match for all of the demographic data. All patients had improved echocardiography parameters, except for the TAPSE and MPA diameter for tadalafil patients. On the other hand, the RVEDd and RVESd were improved better in tadalafil patients, in comparison with the sildenafil group ($p = 0.012$ and 0.022, respectively). There was no significant difference in other echocardiography parameters or the adverse effects.

Conclusions: Using anti-PAH drugs such as tadalafil and sildenafil to hs-PDA patients with PAH does not have additional effect to the acetaminophen. Tadalafil and sildenafil did not vary in efficacy and side effects. Despite the safety of adding anti-

PAH drugs such as sildenafil and tadalafil, the acetaminophen itself can reduce the pulmonary pressure by closing the patent duct.

Abbreviations: 5-PDEI, 5-phosphodiesterase inhibitors; hs-PDA, hemodynamically significant patent ductus arteriosus; NSAID, anti-inflammatory drug; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PDA, patent ductus arteriosus; PPHN, persistent pulmonary hypertension in neonates.

Keywords: Acetaminophen; Echocardiography; Hemodynamically Significant PDA; Patent Ductus Arteriosus; Pulmonary Arterial Hypertension; Sildenafil; Tadalafil.

Introduction

Fetus circulation is mainly dependent on an open ductus arteriosus but the shunt closes after the initiation of breathing. However, the duct does not close in one third of the neonates, usually preterm ones or those with low birth weight.[1] Patent ductus arteriosus (PDA) yields to a left-to-right shunt, yielding to renal and gastrointestinal abnormalities, respiratory distress, intraventricular hemorrhage, intestinal necrosis, and might yield to death if not treated. [2–5]

The clinical diagnostic criteria for PDA include heart murmur, weak pulses, tachycardia, wide pulse pressure, worsening respiration, and need for ventilation.[6] The definite diagnosis is made by echocardiography. The PDA patients are categorized to hemodynamically significant (HS-PDA) and non-hemodynamically significant (non-HS-PDA).[5]

Patients with non-HS-PDA could be treated conservatively but the HS-PDA should be treated with acetaminophen and non-steroid anti-inflammatory drugs (NSAIDs). Prophylactic surgical PDA closure is suggested, which can reduce the intraventricular hemorrhage.[1] Rapid conservative therapy has also shown to be beneficial in reducing the chronic lung diseases, as well as the necrotizing enterocolitis rate.[2]

A standard treatment for PDA consists of appropriate serum therapy while preventing the overload state, using diuretics with cyclooxygenase inhibitors (e.g., indomethacin or ibuprofen) and the surgery is reserved for those with no response to the drug therapy. There are various studies, evaluating the effect of cyclooxygenase inhibitors in closing the PDA.[5]

The 5-phosphodiesterase inhibitors (5-PDEI) such as sildenafil are among the drugs, used in pulmonary artery hypertension (PAH), which can affect the vascular system through their vasodilatory effect, as well as their inhibition on the platelet aggregation and smooth muscle proliferation.[7,8] Inhibiting the 5-phosphodiesterase enzyme can also decrease the pulmonary and systemic pressures in physiological condition with a greater effect on the pulmonary blood pressure in human and animal models of PAH.[9,10] As result, sildenafil is a 5-PDEI considered as an anti-PAH drug with the ability of increasing cardiac index.[1]

On the other hand, some grades of PAH are usually seen in HS-PDA patients. As a result, treating the underlying PAH might improve the patients' response to acetaminophen and NSAID therapy. There are studies reporting persistent PAH in patients undergoing PDA occlusion surgery and the procedure should be performed, cautiously.[15-17] However, lowering the PAH can increase the left-to-right shunt and careful monitoring is needed. Some researchers have suggested that the significant PAH in PDA patients is a multifactorial adverse effect.[16-19]

A recent study suggests that treating the HS-PDA patients with PAH should include sildenafil therapy until the occlusion of the PDA. Otherwise, serious cardiovascular challenges would be expected in patients with PAH.[17] However, there is no consensus in general use of PAP-lowering drugs, including sildenafil. In addition, tadalafil is a newly developed analogues of 5-PDEI with a longer half-life than sildenafil (17.5 hours), which was approved for PAH in 2009.[18] Tadalafil is considered as a safe drug with less side effects than sildenafil, which can improve the functional capacity and oxygenation in adults, as well as the children.[19] This study aims to evaluate the effects of tadalafil and sildenafil on the patients with PDA and PAH.

Methods

This was a randomized clinical trial, conducted on the patients with diagnosed PDA and severe PAH in Akbarabadi Hospital, Tehran, Iran in order to evaluate the effect of adding sildenafil or tadalafil to the regular therapy regimen. The inclusion criteria were: 1) diagnosis of PDA and severe PAH; 2) no additional disease; 3) no immediate improvement despite oxygen supplementation and conservative treatments or having the indication of immediate drug therapy; and 4) a signed written informed consent from the patient's parents

Patients were randomly assigned to three therapeutic groups: Group A: receiving a single dose of 1 mg/kg tadalafil orally plus 5 mg/kg acetaminophen intravenously (IV) every 6 hours; Group B: receiving 1 mg/kg sildenafil orally every 8 hours plus 5 mg/kg acetaminophen IV every 6 hours; Group C: receiving 5 mg/kg acetaminophen IV every 6 hours.

Patients were evaluated by echocardiography before receiving treatment and 72 hours after treatment the PAP, TR, MPA diameter, and RVEDD were measured by an expert neonatal cardiologist, which was blinded to the patients assigned group. The data were labeled as groups A, B and C and data were analyzed by a blinded statistician.

Results

Overall, 96 patients were included in this study with gestational age of 25 to 38 weeks and birth weights of 790 to 3200 grams. The demographic data of the patients in group A (tadalafil), B (sildenafil), and C (acetaminophen) are shown and compared in Table 1. The patients were matched for all of the parameters, except for 5th minute Apgar score. The echocardiography data of the patients are all shown in Table 2.

On the other hand, all of the parameters improved in the tadalafil group after treatment, except for the MPA diameter and the TAPSE. The RVED and RVES parameters were significantly better in the tadalafil group, in comparison with the sildenafil group (*p-values* = .012 and .022, respectively). There was no other difference in the parameters of the patients in three groups.

The complications of the disease are listed in the Table 3. Overall, 3, 5, and 2 patients had one complication in tadalafil, sildenafil, and acetaminophen groups, respectively. One and 3 of the sildenafil and acetaminophen groups and also 2 complications.

Discussion

This was a randomized clinical trial, evaluating the effect of tadalafil or sildenafil addition to acetaminophen therapy in patients with PDA and PAH[20-22]. Among 96 patients enrolled in this study, 32 patients were treated with acetaminophen alone, acetaminophen with sildenafil, or tadalafil[23-25]. The patients were matched by their demographic data, as well. 72 hours after getting the treatment, all parameters were improved in the tadalafil group, except for the TAPSE and MPA diameter[26-28]. In the comparison between the tadalafil and sildenafil groups, the RVED and RVES parameters were improved better in the patients receiving tadalafil (p = 0.012 and 0.022, respectively)[30-33]. There was no other difference in the groups regarding their response to treatment.

Other study on 32 patients with persistent pulmonary hypertension in neonates (PPHN) was performed in 2017[34-36]. The researchers compared the effect of sildenafil and tadalafil on the echocardiography parameters of the patients in 6 months. The researchers showed that the both 5-PDEI drugs improved TR, RVEDD, and MPA with no significant difference.[20] This study showed similar non-inferiority of tadalafil to sildenafil in improving the echocardiography findings. However, the RVED and RVES had better response to treatment with tadalafil in the current study. In addition, 3 and 7 of the patients in tadalafil and sildenafil groups had at least one complication in this study, respectively. Considering the non-inferiority of the tadalafil to sildenafil, it could be considered as a better alternative in patients with pulmonary hypertension[37-39].

Current study had some limitations, including low population and limited spectrum of the patients. It is important to compare the side effects of tadalafil and sildenafil, precisely. On the other hand, other etiologies of pulmonary hypertension are potential opportunities to compare the effects of tadalafil and sildenafil[40-42].

This study aimed to evaluate the efficacy of using anti-PAH drugs in patients with hs-PDA and PAH. Reducing the pulmonary artery blood pressure has the risk of increasing the left-to-right shunt and the consequent heart failure but the use of acetaminophen in this study reduces that risk. Acetaminophen is used as to close the patent duct for years,[12,13] but alleviating the consequent PAH in the hs-PDA patients could have a positive impact on the treatment. Drugs like sildenafil are shown as pulmonary blood pressure reducing agent in neonates, specially those with persistent pulmonary hypertension.[1,2,5] There was no difference between using acetaminophen, and acetaminophen with a 5-PPDI in this study. It is probably because the PAH is mainly due to the PDA and no other additional reason. The PAH seen in PDA is due to the overflow of the blood stream to the lungs, similar to the process seen in VSD patients. However, the anti-PAH drugs are beneficial in older VSD patients, because of the consequent damage to the pulmonary arterioles. Delay in anti-PAH therapy may yield to the Eisenmenger syndrome, if not treated.[21] But the high pulmonary blood pressure besides delayed maturation in pulmonary vessels does not yield to any damage, before closing the ductus. The PAH was resolved in the acetaminophen group in this study[43], as well as the groups receiving sildenafil or tadalafil, besides the acetaminophen. It can be concluded that the addition of a 5-PPDI does not yield to additional benefit[44], when added to acetaminophen. On the other hand, there was no general difference between the sildenafil and tadalafil patients. Further studies are needed for evaluating the sildenafil and tadalafil among neonates and children[45-47]. Overall, using 5-PPDIs like sildenafil and tadalafil are not suggested in addition to acetaminophen in hs-PDA patients[48-50].

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at ur institution. All patients and/or parents/caregiver(s) provided written informed consent and/or assent (as applicable) at enrollment.

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Table 1. Demographic Data of the Patients

	GROUP A	GROUP B	GROUP C	p-value
Sex,n	Male:22 Female:10	Male: 13 Female:19	Male: 18 Female:14	**0.397***
Delivery,n	C/S: 20 NVD: 12	C/S: 20 NVD: 12	C/S: 20 NVD: 12	**1.00***
Steroid before labor,n	24	16	13	**0.121***
Gestational Age,wk	32.14±2.85	32.47±3.19	30.92±2.72	**0.372**†
Birth Weight,gr	1719±438	1891±602	1702±714	**0.201**†
Birth Apgar Score	4.71±1.89	5.90±2.19	5.73±1.68	**0.293**†
Apgar in 5th Minute	6.47±1.64	8.42±1.21	8.11±1.07	**0.018** †

Define C/S, C-section; Group A, Tadalafil + Acetaminophen; Group B, Sildenafil + Acetaminophen; Group C: Acetaminophen; NVD, non-vaginal delivery

*Chi-squared test

†Mann-Whitney test

Table 2. The Echocardiography Parameters of the Patients Their Comparison Between Groups After Treatment

P_Value *			Group			Studied Parameter	
Group A vs C	Group B vs C	Group A vs B	Group C	Group B	Group A		
0.204	0.98	0.29	15.61 (±1.95)	16.51 (±1.32)	15.21 (±1.61)	***Before***	**RV1**
0.139	0.721	0.08	11.19 (±2.51)	11.92 (±1.69)	9.63 (±2.94)	***After***	
			0.002	0.001	0.006	p-value†	
0.840	0.621	0.623	13.81 (±2.95)	14.39 (±2.21)	13.32 (±2.19)	***Before***	**RV2**
0.520	0.781	0.441	10.18 (±3.61)	10.82 (±2.67)	8.91 (±2.89)	***After***	
			0.004	0.002	0.006	p-value†	
0.939	0.621	0.687	24.49 (±3.42)	24.69 (±3.01)	25.21 (±3.18)	***Before***	**RV3**
0.256	0.375	0.828	18.41 (±3.34)	20.25 (±3.48)	19.43 (±1.93)	***After***	
			0.003	0.006	0.003	p-value†	
0.461	0.035	0.160	1.51 (±0.18)	1.59 (±0.16)	1.72 (±0.17)	***Before***	**RV/LV Systolic Diastolic Ratio**
0.274	0.098	0.476	1.16 (±0.16)	1.30 (±0.25)	1.36 (±0.21)	***After***	
			0.003	0.005	0.008	p-value†	

0.405	0.681	0.339	0.507 (±0.132)	0.531 (±0.170)	4.73 (±13.51)	***Before***	**TAPSE**
0.920	0.223	0.581	0.748 (±0.232)	0.720 (±0.253)	0.614 (±0.194)	***After***	
			0.004	0.009	0.118	p-value†	
0.795	0.869	0.885	56.92 (±11.07)	56.53 (±7.03)	55.72 (±6.60)	***Before***	**TRPG**
0.258	0.107	0.557	35.69 (±10.24)	40.78 (±12.61)	41.34 (±9.91)	***After***	
			0.003	0.002	0.008	p-value †	
0.429	0.841	0.572	3.71 (±1.83)	4.69 (±2.41)	4.32 (±1.05)	***Before***	**MPA diameter**
0.284	0.212	0.849	3.28 (±1.21)	3.79 (±1.88)	6.18 (±7.72)	***After***	
			0.092	0.017	0.126	p-value†	
0.220	0.062	0.503	25.89 (±5.29)	28.34 (±4.81)	29.47 (±4.04)	***Before***	**PIPGmax**
0.354	0.437	0.620	17.91 (±5.31)	21.0 (±8.04)	19.7 (±6.75)	***After***	
			0.003	0.003	0.005	p-value†	
0.772	0.574	0.075	3.48 (±1.32)	3.61 (±0.81)	3.06 (±0.65)	***Before***	**RVEDd**
0.184	0.566	0.012	2.64 (±0.91)	3.18 (±0.87)	2.23 (±0.32)	***After***	
			0.003	0.006	0.011	p-value†	
0.908	0.597	0.165	2.37 (±0.75)	2.46 (±0.42)	2.21 (±0.71)	***Before***	**RVESd**
0.371	0.285	0.022	1.71 (±0.60)	2.03 (±0.41)	1.61 (±0.35)	***After***	
			0.003	0.012	0.007	p-value†	

Group A, Tadalafil + Acetaminophen; Group B, Sildenafil + Acetaminophen; Group C: Acetaminophen

*. Mann-Whitney test

†. Wilcoxon test

Table 3. Complications of the Patients

***Complicat*ions**	**Acetaminophen**	**Sildenafil**	**Tadalafil**
Hypoperfusion	0	2	**3**
ROP	4	2	**0**
GIB	1	1	**0**
NEC	0	0	**0**
Pulmonary Hemorrhage	0	1	**0**
BPD	2	1	**0**

IVH	0	0	**0**
Sepsis	1	0	**0**

BPD, ; GIB, ; Group A, Tadalafil + Acetaminophen; Group B, Sildenafil + Acetaminophen; Group C: Acetaminophen; IVH, ; NEC, ; ROP,