

Additive Effect of Phosphodiesterase Inhibitors in Control of Pulmonary Hypertension after Congenital Cardiac Surgery in Children

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Received: Feb 06, 2012; Accepted: Aug 04, 2012; First Online Available: Nov 05, 2012

Abstract

Objective: Control of residual pulmonary arterial hypertension (PAH) after closure of left to right shunts in children is still a challenging issue. The purpose of this study was to compare the effect of two phosphodiesterase inhibitors in pediatric cardiac surgical patients.

Methods: A total of 48 postoperative children were enrolled in the study between 2008 and 2010. Patients were stratified based upon choice of pulmonary vasodilator into three equal groups (n=16); Milrinone group received intravenous milrinone (0.75 µ/kg/min), Sildenafil group received oral sildenafil (0.3 mg/kg every 3 hours) and the Combination group received both medications.

Findings: Demographic variables and types of congenital anomalies were not different among the 3 groups. Patients in the Combination group had higher preoperative pulmonary artery to aortic (PA/AO) pressure ratios compared to other two groups ($P=0.001$). Postoperatively, patients in Milrinone group incurred lower systolic PA and PA/AO pressures compared to Sildenafil group ($P=0.014, 0.003$), but it was the same in Sildenafil and Combination group ($P=0.2; 0.330$ respectively). Pulmonary hypertensive crisis was noted in 6 patients in Sildenafil group, and 3 patients in Combination group ($P=0.02$). Significant rise in PA pressure was noticed after discontinuation of drug in Milrinone group ($P=0.001$), which was not observed in the Combination group ($P=0.6$). No mortality was noticed in any of the groups.

Conclusion: Intravenous milrinone is more effective than oral sildenafil in control of postoperative PAH and elimination of pulmonary hypertensive crisis. Combination of two drugs reduces the risk of rebound pulmonary arterial hypertension after discontinuation of milrinone.

Iranian Journal of Pediatrics, Volume 23 (Number 1), February 2013, Pages: 19-26

Key Words: Phosphodiesterase Inhibitors; Pulmonary arterial hypertension; Cardiac surgery; Children

Introduction

Closure of large left to right cardiac shunts with preexisting significant pulmonary arterial hypertension (PAH) is usually accompanied by the hazards of post-operative residual PAH, pulmonary hypertensive crisis and right ventricular dysfunction. Different pulmonary

vasodilators have been used to treat high postoperative pulmonary artery (PA) pressure and minimize related adverse consequences. Sildenafil, an oral selective phosphodiesterase inhibitor (PDEI) type 5, is proven to have pulmonary vasodilatory effect in various types of pulmonary hypertension (PH) in children and adults^[1-5]. Another potential therapeutic option,

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intravenous or nebulized milrinone, is a selective type 3 PDEI, which has successfully been used in children with high PA pressure^[6-8]. Few studies have compared the isolated use of either of the medications on post-operative PAH in children. The aim of this prospectively designed study was to compare the efficacy of monotherapy with either of the drugs and the combination therapy on PA pressure regulation after pediatric cardiac surgery. We hypothesized that combination of Sildenafil and Milrinone provides superior vasodilatory and consequent anti-pulmonary hypertensive effects in patients with congenital defects.

Subjects and Methods

Patients and study design: The institutional review board approved this study. Prospectively, from pediatric patients with preoperative echocardiographic diagnosis of PAH [tricuspid regurgitation (TR) gradient >30mmHg] due to large left to right cardiac shunts who had surgical closure of their shunts those with significant PAH, defined as intraoperative directly measured PA to aortic pressure ratio equal or greater than 0.6, were included in the study. A total of 48 patients met the inclusion criteria. Thirty-two patients with intraoperative pulmonary artery to aortic (PA/AO) pressure between 0.60-0.84 were randomly assigned into 2 groups (n=16) to receive either Milrinone or Sildenafil. The third group consisted of higher risk patients with near systemic PA pressure defined as intraoperative PA/AO pressure equal or greater than 0.85, received a combination therapy with both Milrinone and Sildenafil. Patients' characteristics are summarized in Table 1. The three groups were compared on the basis of preoperative general characteristics, intra- and postoperative PA to aortic pressure ratio, PA and systemic pressures, duration of ICU and hospital stay and postoperative complications including pulmonary hypertensive crisis and mortality. Preoperative transthoracic echocardiography (TTE) was used for confirming diagnoses, and direct intraoperative PA and aortic pressure measurements for assessment of the severity of pulmonary arterial

hypertension.

Drug administration: Patients in Milrinone group received intravenous milrinone, 50 µg/kg stat before initiation of cardiopulmonary bypass, followed by 0.75 µg/kg/min for 36 hours after entry into the intensive care unit (ICU). The drug was then tapered and discontinued within 4 hours. Patients in Sildenafil group were administered Sildenafil, 0.3 mg/kg every three hours by nasogastric or oral route started before the initiation of cardiopulmonary bypass and continued throughout the hospital stay. Combination group, consisting of sixteen patients with near systemic intraoperative PAH, received a combination of the drugs.

Postoperative assessment of pulmonary arterial hypertension: Monitoring of PA pressure (PAP) through intraoperatively placed PA lines were the mainstay of pressure monitoring in this study. PAP was continuously measured for the first 48 hours of ICU stay and monitoring lines were removed thereafter. Daily monitoring of PAP was then performed with TTE until patients were discharged from the hospital.

Statistical methods: SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Quantitative values were expressed as mean±standard deviation and range and qualitative values as number and percent. Student t-test, Chi square and ANOVA were utilized for multiple comparisons. *P* values less than 0.05 were considered as significant.

Findings

Forty-eight patients, 19 (39.6%) males, were included in this study with mean age of 17.04±26.73 mo (range 3-144 mo) and mean weight of 7.42±4.64 kg (range 3.8-29 kg). Out of a total of 48 patients, there were 40 with ventricular septal defect (VSD), 6 with atrioventricular septal defect (AVSD), and 2 with aortopulmonary window (APW). The mean gradient across VSD or aortopulmonary window was 17.1±10.4 mmHg and mean TR gradient was 64.2±15.7 mmHg. Mean intraoperative PA to aortic pressure ratio was 0.82±0.16 (range 0.60-1.25).

Table 1: Demographic and preoperative variables in three groups

Parameter*	Milrinone (G1)	Sildenafil (G2)	Combination (G3)	P. value
Sex (Male) (Frequency)	3 (18.8%)	8 (50%)	8 (50%)	0.1
Age (mo)	12.3 (11.6)	13.5 (12.9)	25.4 (42.7)	0.3
Weight (Kg)	6.2 (2.3)	7.1 (3.1)	8.9 (7.0)	0.2
Body surface area (m ²)	0.36 (0.08)	0.38 (0.18)	0.44 (0.23)	0.3
VSD gradient (mmHg)	15.9 (10.0)	20.2 (13.0)	15.8 (8.3)	0.5
TR gradient (mmHg)	67.4 (20.0)	63.9 (13.4)	60.8 (14.1)	0.8
Intraoperative PA/AO pressure	0.78 (0.14)	0.74 (0.15)	0.94 (0.13)	0.001‡

* All parameter were presented as Mean (Standard deviation); ‡ Group P. value: 1, 2: 0.5; 1, 3: 0.002; 2, 3: 0.001
VSD: Ventricular Septal Defect; TR: Tricuspid Regurgitation; PA/AO: Pulmonary Artery to Aortic

Group 1 (Sildenafil group) consisted of 16 patients, 3 (18.8%) males, with mean age of 12.3±11.6 mo (range 5-48 mo) and mean weight of 7.1±3.1 kg (range 3.8-15 kg). The CHD diagnosis was VSD, ASD or PDA in 13 patients and three patients had AVSD. Intraoperative PA/AO pressure ratio was 0.78±0.14 (range 0.62-0.84).

Group 2 (Milrinone group) included 16 patients, 8 (50%) males, with mean age of 13.5±12.9 mo (range 4-48 mo) and mean weight of 7.1±3.1 kg (range 3.8-15 kg). All of the patients in this group had VSD, ASD or PDA. Intraoperative PA/AO pressure ratio was 0.74±0.15 (range 0.60-0.81).

Group 3 (Combination group) consisted of 16 patients, 8 (50%) males, with mean age of 25.4±42.7 mo (range 3-144 mo) and mean weight of 8.9±7.0 kg (range 4.4-29 kg). 11 patients in this group had VSD, ASD or PDA and 2 patients had APW. Intraoperative PA/AO pressure ratio in this group was 0.94±0.13 (range 0.85-1.25).

Table 1 summarizes patients' demographic and preoperative variables in each group. There were no significant differences between the three groups on the basis of age, weight, body surface

area, sex, VSD and tricuspid regurgitation gradients. Intraoperative PA/AO pressure in Combination group, who received both medications, was near systemic (0.92±0.13) and significantly higher than in Milrinone and Sildenafil groups ($P=0.001$).

As shown in Table 2, postoperative continuous PA pressure monitoring showed significant difference in systolic PA and PA/AO pressures between the three groups with lower values in Milrinone group, and similar values in the other two groups, despite significantly higher preoperative PAH in Combination group (Fig. 1 and 2). There were no significant differences in diastolic and mean PA pressures among the three groups. Neither the occurrence of systemic hypotension, nor the aortic pressure showed significant difference among the three groups (aortic pressures, 93.4 vs. 92.0 vs. 94.5, respectively).

A significant systolic PAP rise was noticed upon discontinuation of the drug in Milrinone group (27 vs. 22 mmHg, $P=0.001$), which was not seen in the patients of the combination therapy group. (37.3

Table 2: Postoperative pressure measurements in three groups

Parameter	Milrinone (G1)	Sildenafil (G2)	Combination (G3)	P. value	Group P. value
Systolic PA pressure (mmHg) (Range)	24.1 (7.6) (16.4-50.2)	30.4 (5.9) (21.2-43.1)	33.9(9.2) (21.1-52.3)	0.003	1,2: 0.014 1,3: 0.003 2,3: 0.206
Diastolic PA pressure (mmHg) (Range)	10.7 (7.9) (3.8-37.5)	10.5 (4.4) (5.9-18.9)	14.1 (6.1) (4.5-27)	0.2	
Mean PA pressure (mmHg) (Range)	15.1 (7.5) (8.1-41.1)	17.1 (4.5) (10.9-25.2)	20.6 (7.1) (9.9-35.6)	0.06	
Systolic AO pressure (mmHg) (Range)	93.4 (11.7) (68.6-112.7)	92.0 (10.2) (70.9-104.9)	94.5 (15.4) (67.4-125.2)	0.85	
Systolic PA/AO pressure (Range)	0.26 (0.06) (0.15-0.45)	0.33±0.07 (0.21-0.47)	0.36 (0.10) (0.2-0.59)	0.002	1,2: 0.003 1,3: 0.001 2,3: 0.330

PA: Pulmonary Artery; AO: Aortic

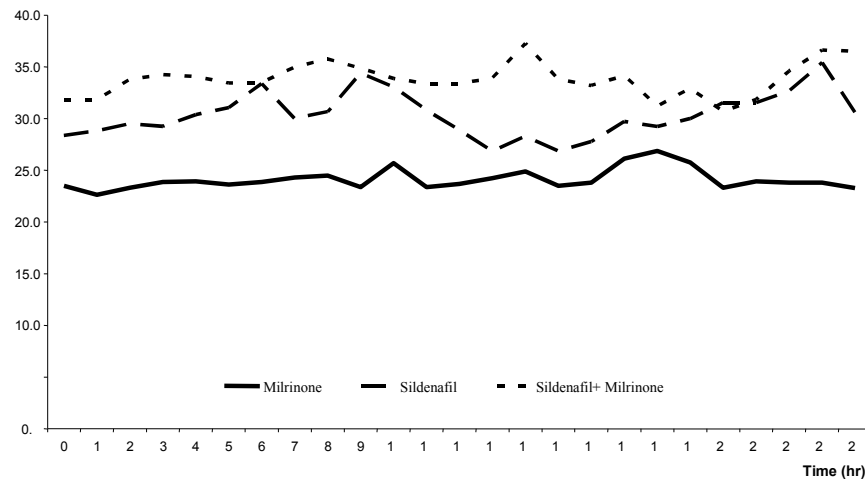


Fig. 1: Systolic pulmonary artery pressure in 3 groups in the first 24 hours after surgery

vs. 34.5 mmHg, $P=0.6$) (Table 3). Pulmonary hypertensive crisis was not demonstrated in any of Milrinone group patients but six (37.5%) patients in Sildenafil group and 3 (18.8%) patients in Combination group developed crises ($P=0.02$). The crisis was transient in 3 patients of the Sildenafil group, but milrinone had to be administered with the same maintenance dosage in the other 3. In Combination group, episodes of crisis occurred during tracheal suctioning of secretions with no need to administration of medications.

Length of ICU stay was significantly shorter in Milrinone group compared to Sildenafil and Combination group ($P=0.04$, Table 4). However, there was no statistically significant difference in the total hospital stay among the 3 groups. There were no mortalities in either group.

Discussion

Pulmonary hypertension has been defined as a resting mean pulmonary arterial pressure (mPAP) more than 25 mmHg, or an mPAP with exercise more than 30 mmHg in cardiac catheterization. The subgroup of PH known as pulmonary arterial hypertension, adds the criterion that the pulmonary arterial wedge pressure must be equal to or less than 15 mmHg. Some definitions have also included pulmonary vascular resistance (PVR), requiring that it be ≥ 2 or 3 Wood units. With the introduction of Doppler echocardiography, approximate evaluation of PAP became feasible. In the presence of a tricuspid insufficiency peak gradient (TIPG) ≥ 30 mmHg, some investigators have used arbitrary criteria for noninvasive diagnosis of PH. During a meeting on

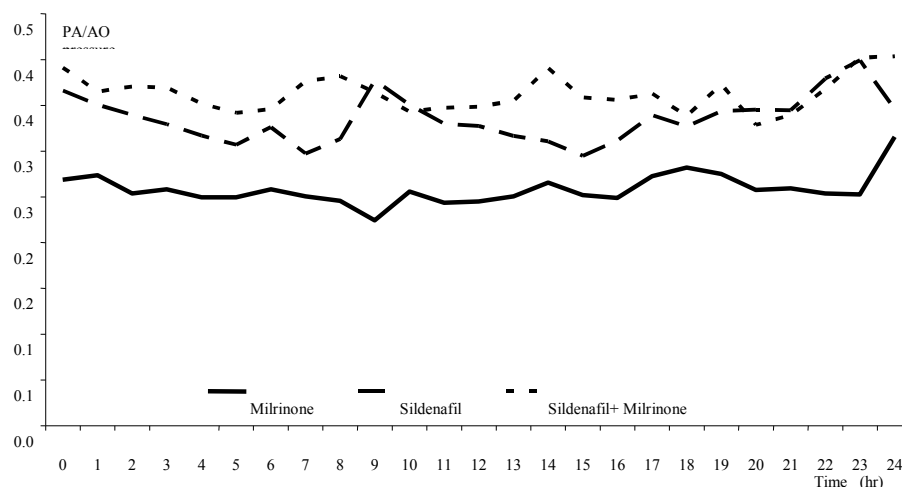


Fig. 2: Systolic pulmonary artery to aortic pressure in 3 groups in the first 24 hours after surgery

Table 3: Pulmonary artery pressures after discontinuation of milrinone

Pressure	Milrinone (G1)		P. value	Combination (G3)		P. value
	On Milrinone	D/C Milrinone		On Milrinone	D/C Milrinone	
Systolic (mmHg)	22.0 (2.9)	27.0 (6.2)	0.001	34.5 (10.9)	37.3 (15.7)	0.6
Diastolic (mmHg)	8.5 (3.3)	12.4 (7.0)	0.003	14.4 (7.4)	15.9 (9.5)	0.7
Mean (mmHg)	15.4 (8.1)	20.0 (0.9)	0.05	22.4 (9.9)	23.1 (11.5)	0.9

PH held in Evian, France, in 1998, mild PH was arbitrarily defined as a tricuspid jet velocity (TJV) 2.8 to 3.4 m/s, which corresponds to TIPG 31 to 46 mmHg and to PAP 36 to 51 mmHg, if a fixed right atrial pressure (RAP) estimate of 5 mmHg is used. It seems reasonable to consider TJV >2.8 m/s and TIPG \geq 31 mmHg at rest as elevated, except in elderly and/or very obese patients^[9]. In this study preoperative diagnosis of PAH was based on Doppler echocardiographic measurements.

Post-operative residual PAH is accompanied by the risk of pulmonary hypertensive crisis and right ventricular dysfunction. Different pulmonary vasodilators have been used for prevention or treatment of these complications. PDEI's, like sildenafil and milrinone, are among the most common studied pulmonary vasodilators, but there are little studies about using a combination of two PDEI drugs in patients with the risk of postoperative PH crisis.

In this study, we have shown that both intravenous milrinone and oral sildenafil are effective pulmonary vasodilators. We demonstrated that intravenous milrinone was superior to oral sildenafil to control postoperative PA pressure and successfully decreased the risk of pulmonary hypertensive crisis. In addition, patients with very high preoperative PA pressure incurred to benefit the most from combination of both drugs. Furthermore, our data suggest that

occurrence of rebound PAH after discontinuation of milrinone, can be prevented by addition of sildenafil during tapering period of milrinone.

Residual PAH following the surgical closure of large left to right shunts may cause significant postoperative hemodynamic instability, and in occasions death, if uncontrolled PAH crisis occurs. Since right ventricle is more sensitive to afterload changes than left ventricle, right ventricular dysfunction in such patients is another potential postoperative hazard, particularly when pump time is prolonged or acute increase in PA pressure has occurred^[10]. Therefore, controlling PAP is extremely important to minimize morbidity and mortality after such congenital cardiac operations. Suggested treatment algorithm for PAH following cardiac surgery includes inhaled nitric oxide (iNO), milrinone, sildenafil, and short term use of inhaled or intravenous prostanoids^[9,10]. Inhaled NO is a potent pulmonary vasodilator without systemic vasodilatory effect. The need for special equipments to administer the drug and the risk of occurrence of rebound PAH following discontinuation limits the regular use of this therapeutic option^[10,12]. Combination of iNO with other agents such as sildenafil^[13,14], milrinone^[15,16] or dobutamine^[17] has been reportedly more efficient to control postoperative PH.

Milrinone is a selective PDEI type 3 with inotropic and vasodilatory effects. This drug

Table 4: Postoperative course in three groups

Course	Milrinone (G1)	Sildenafil (G2)	Combination (G3)	P-value	Group P-value
ICU stay (Hour) (Range)	68 (25) (40-144)	108 (65) (46-288)	120 (78) (65-340)	0.04	1,2: 0.02 1,3: 0.01 2,3: 0.63
Hospital stay (Day) (Range)	5.5 (1.7) (4-10)	8.5 (6.4) (5-30)	7.9 (4.7) (4-22)	0.2	--
PH Crisis No (%)	0 (0)	6 (37.5)	3 (18.8)	0.02	1,2: 0.01 1,3: 0.22 2,3: 0.43
Mortality No (%)	0 (0)	0 (0)	0 (0)	1.0	--

ICU: Intensive Care Unit; PH: Pulmonary Hypertension

significantly reduces pulmonary vascular resistance and improves right ventricular function. However, systemic hypotension has been reported to limit the use of this drug^[6-7,10]. Sildenafil, a selective PDEI type 5, is effective for the treatment of acute and chronic PAH with minimal systemic vasodilatory effect. It is favored for the use in pediatric patients because of its rapid onset of action, good absorption after oral intake and minimal side effects^[2,5,10]. Factors limiting its use are its availability in only oral form and the risk of severe systemic hypotension when used concomitantly with nitrates^[10].

In an animal study by Matot et al^[18], intravenous zaprinast, another PDEI type 5, is shown to have greater pulmonary vasodilatory effect than intravenous milrinone. Urdaneta and colleagues^[19], in another animal study compared pulmonary vasodilatory effect of UK 343-664, an intravenous sildenafil analogue, with intravenous milrinone. The two drugs had the same efficacy with higher pulmonary selectivity of UK 343-644. In the current study, pediatric patients who received intravenous milrinone were shown to have significantly lower postoperative systolic PA and PA/AO pressures than those who received oral sildenafil. Furthermore, PH crisis occurred in 6 patients in the sildenafil group, whereas those who received milrinone remained free of crisis.

In the study by Lobato and associates^[20], independent action and additive effect of sildenafil and milrinone during thromboxane-induced acute pulmonary arterial hypertension were shown in a porcine model. The combination of drugs achieved a better hemodynamic profile with greater pulmonary vasodilatation and increased contractility without additional systemic vasodilatation. In our study, combination of milrinone and sildenafil in Combination group, who had significantly higher preoperative PAH, resulted in postoperative PA pressures comparable to those who were on sildenafil and had lower preoperative PAH. In addition, incidence of PH crisis was lower in the combination group compared to those who received sildenafil, despite near-systemic preoperative PAH. Therefore, combination of the two drugs may have additive effects on the control of postoperative PA pressure.

In this study, patients in the Milrinone-only group, developed significant rise of PA pressure

upon tapering and discontinuation of the drug - an event not seen in the Combination group. The rebound PAH phenomenon and the protective effect seen with concomitant administration of sildenafil, may be a strong evidence of the benefit gained by addition of sildenafil in cases of severe PAH. Our finding is consistent with those of Trachte et al^[21], which showed sustained pulmonary vasodilatory effect of sildenafil, facilitating weaning of iNO, and milrinone, nitroglycerine and sodium nitroprusside when used as adjunctive therapy. In another study by Namachivayam et al^[22] a single dose of oral sildenafil prevented rebound after withdrawal of iNO. Prophylactic sildenafil administration during weaning from iNO was suggested as an effective strategy in that study. Lee et al^[23], have also shown facilitated withdrawal of iNO and prevention of rebound pulmonary arterial hypertension with concomitant use of oral sildenafil after congenital cardiac surgery in children.

Continuous monitoring of systemic pressure in the Milrinone group, or the Combination group failed to reveal significant drop in aortic pressure. This finding was consistent with the study by Lobato and coworkers^[20], who showed that combination of the drugs was not accompanied by additional systemic vasodilatation. In contrary, there are available reports that consider systemic hypotension as a limiting factor for administration of milrinone^[6-7,10].

In the current study, low cardiac output state and the need for inotropes were similar in the three groups. Lobato et al^[20] showed improved cardiac output and right ventricular function with combined use of milrinone and sildenafil. In that study sildenafil alone had no effect on right ventricular function. However, Madden^[24] et al describe two postoperative cases with significant reduction in pulmonary vascular resistance and rise in systemic blood pressure after administration of oral sildenafil. Authors suggested that sildenafil should be considered for the management of selected patients with pulmonary arterial hypertension who develop right ventricular dysfunction at induction or during cardiac surgery. Gan et al^[25] also showed that sildenafil alone can improve right ventricular diastolic and systolic function by reducing right ventricular afterload.

The ICU stay was demonstrated to be lower in Milrinone group in this study, but it was the same in Combination group and Sildenafil group, despite more severe PAH in Combination group.

Patients in the current study did not develop any drug related complications and there was no mortality, both findings point at the proposed effective role of milrinone and sildenafil in decreasing mortality and morbidity after closure of large left to right shunts with preexisting PAH, even in near systemic levels. This is consistent with our initial hypothesis.

The main limitation to this study was the non-randomized assignment of patients in the third group to receive the combination therapy. This was based on ethical considerations, and the fact that patients with exceedingly high, near-systemic PA pressures were considered for combination therapy. However, this did not affect random assignment of patients into Milrinone-only or Sildenafil-only groups. In addition, preoperative cardiac catheterization was not performed in this study and echocardiography and direct intraoperative measurements of pressure were the mainstays for estimation of severity of PAH. Larger studies are needed to confirm the results of this study.

Conclusion

In conclusion, this study shows that both intravenous milrinone and oral sildenafil are effective pulmonary vasodilators and can improve surgical outcome and decrease mortality after closure of large left to right shunts in children. Intravenous milrinone was shown to have superiority to oral sildenafil in the control of postoperative high PA pressure and the decrease of pulmonary hypertensive crisis occurrence. In patients with very high preoperative PAH, combination of both drugs incurred to have additive effects. For prevention of rebound PAH after discontinuation of milrinone, administration of sildenafil during the tapering period of milrinone may be helpful.

Acknowledgment

We want to thank the valuable contribution of all anesthesiologists, perfusionists and cardiac surgery ICU nurses in Dena hospital, Shiraz in perioperative care of our patients.

Conflict of Interest: None

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