Comparative study between the efficacy of Intravenous Immunoglobulin alone versus the efficacy of Intravenous Immunoglobulin combined with Steroids in treatment of Acute Myocarditis in Pediatric patients in Qena University Hospital

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Abstract
Background: High-dose immunosuppressive steroids may help myocarditis regain left ventricular systolic function. Steroid therapy effects are disputed. Evidence suggests IVIG, which works in immune-mediated disorders, may treat acute myocarditis.
Objectives: Comparing the efficacy of IVIG alone versus the efficacy of IVIG combined with steroids in treatment of acute myocarditis in pediatric patients.
Patients and methods: This study included pediatric cases with myocarditis diagnosed using clinical, echocardiographic, electrocardiographic, and enzyme tests. Patients who consent to IVIG or IVIG with pulse steroids were included. Group-1 (IVIG alone) and Group-2 (IVIG plus steroids) were evaluated at presentation, one week, and one month. A complete history, Modified Ross heart failure classification, CK-MB, Troponin-I, ECG, and echocardiogram were done.
Results: The median patient age was 2.1years (range:1day–11years), 70% were males, and 80 % were rural. There was in-significant difference regarding Ross classification at time of diagnosis. Ross class I was in 73.53% after one month (p=0.003). After one week, there was significant difference regarding Troponin levels (p=0.049) with range of 0.02-30 ng/ml, and there was significant difference (p=0.010) between the 2 groups regarding the incidence of abnormal rhythm which affected 47.37% in group (1) compared to 10% in group (2). After one month, there was significant difference regarding Troponin levels (p=0.014) with range of 0.01-12 ng/ml. There was significant difference (p=0.019), regarding fraction shortening which was higher in Group 2 (35.83±3.76) compared to Group 1 (31.25±5.87).
Conclusion: Combining steroids with IVIG is more advantageous than receiving IVIG alone in treating pediatric acute myocarditis.
Keyword: Acute myocarditis; IVIG; Steroids; Pediatrics.
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Introduction

Acute myocarditis is a critical inflammatory condition affecting the myocardium, particularly prevalent among pediatric patients **(Tunuguntla et al., 2019).** It presents a unique set of challenges, given the potential for a wide range of clinical manifestations, including heart failure, arrhythmias, and even sudden cardiac death. The pediatric population is particularly susceptible to this condition, making its prompt and effective management a matter of utmost importance. A variety of treatment strategies have been explored to address this complex clinical scenario **(Ammirati et al., 2021; Tschöpe et al., 2021).**

Intravenous immunoglobulin (IVIG) has gained recognition for its immunomodulatory and anti-inflammatory properties, making it an attractive option for managing acute myocarditis. While its role in addressing various autoimmune and inflammatory conditions is well-established, its specific effectiveness in the context of pediatric myocarditis remains an area of ongoing investigation. This study aims to shed light on the efficacy of IVIG as a standalone treatment option for acute myocarditis in pediatric patients **(Robinson et al., 2020).**

Steroids have been employed in a multitude of medical conditions. Their use has been explored in the context of myocarditis, raising the prospect of enhanced anti-inflammatory intervention. This research investigates the efficacy of steroids in treating acute myocarditis in pediatric patients and the potential for their combination with IVIG to yield improved outcomes **(Cheng et al., 2021).**

The combination of IVIG with steroids presents an intriguing therapeutic strategy for pediatric myocarditis. The synergy between the immunomodulatory effects of IVIG and the anti-inflammatory properties of steroids may offer a more comprehensive and effective approach for managing this condition **(Li et al., 2019).**

The main aim of the study was to compare the outcomes and clinical parameters of pediatric patients treated with IVIG alone versus those treated with the combination of IVIG and steroids.

Patients and methods

The research encompasses a randomized clinical trial conducted at Qena University Hospital, employing specific research methods and techniques. The study focuses on patients in the pediatric department who exhibit symptoms suggestive of myocarditis diagnosed through clinical evaluation, Echocardiography, Electrocardiography, and enzyme analysis. The inclusion criteria involve patients who have received IVIG or IVIG followed by pulse steroids and consent to participate in the study.

Exclusion criteria consist of patients who died before diagnosis or treatment and those for whom consent was not obtained. The sample size calculation incorporates two groups: Group 1, consisting of 20 patients receiving IVIG alone, and Group 2, comprising 20 patients receiving IVIG followed by pulse therapy of steroids. Assessment of both groups involves evaluating clinical presentations and investigations (laboratory and imaging) at presentation, after one week, and after one month.

The study employs various tools, including a detailed history and examination, along with the Modified Ross heart failure classification for children **(Ross, 2012).** This classification encompasses different classes based on symptoms observed in infants and older children. Investigative measures involve CK-MB, Troponin I with (TOSOH AIA-360, TOSH Bioscience, South San Francisco, USA), Electrocardiography (Nihon kohden ECG 2150, Nihon Kohden, Tokyo, Japan) and Echocardiography (vivid

s5, General Electric Healthcare, Chicago, USA).

The primary research outcome measure aims to study the efficacy of IVIG in treating acute myocarditis in pediatric patients at Qena University Hospital. Secondary outcomes focus on assessing the efficacy of IVIG followed by pulse steroids in the treatment of acute myocarditis in the same patient population within the pediatric department at Qena University Hospital.

Ethical Code: SVU-MED-PED025-1-22-3-359

Statistical analysis

The statistical analysis of the data was conducted utilizing the Statistics Package for Social Sciences (SPSS) version 26, developed by SPSS Inc. in Chicago, IL, USA. Prior to analysis, normality testing, including the Kolmogorov-Smirnov and Shapiro-Wilk tests, was performed, revealing that the data did not exhibit a normal distribution. Categorical variables were characterized by their respective numbers and percentages (N, %), and the statistical analysis involved the application of the Chi-square test and Fisher exact test. Continuous data were presented by indicating the minimum and maximum values, mean with standard deviation (SD), or median with the first quartile to the third quartile range. To compare non-related samples within each pair of groups, the Mann-Whitney test was employed. Significance levels were determined with a two-tailed p-value, where a value less than 0.05 was considered indicative of a statistically significant difference. This rigorous statistical approach ensured a comprehensive analysis of the data, providing robust insights into the observed trends and relationships within the study parameters.

Results

As regard demographic data in our study, the predominant findings include a median age of 2.1 years (range: 1 day - 11 years), with 70% of the cases being males and 80% originating from rural areas. Moreover, 70% of the cases had a low socioeconomic status, and 92.5% received care in the Pediatric Intensive Care Unit (PICU) while 7.5% were in the Neonatal Intensive Care Unit (NICU). (**Table.1**).

Table 1. Demographic data of the studied cases

Variables	Total
	n=40
Age (years)	
Range	1day – 11yrs
Median(Q1-Q3)	2.1(0.459-7)
Sex	
Male	28(70%)
Female	12(30%)
Residence	
Urban	8(20%)
Rural	32(80%)
Socioeconomic	
Low Moderate High	28(70%) 7(17.5%) 5(12.5%)
Site	
NICU	3(7.5%)
PICU	37(92.5%)

Ross classification at diagnosis showed no significant difference between groups. However, one week later, there was a significant shift in Ross classifications (p = 0.036*), and after one month, Ross class I dominated significantly at 73.53% (p = 0.003**). Survival analysis at one week and one month showed no significant differences between the groups. (**Table. 2**)

Table 2. Comparison between the studied groups regarding the changes in Ross classification along the study period

Variables	Group 1 (IVIG)	Group 2 (Steroid and IVIG)	
Ross classification			
At time of diagnosis	n=20	n=20	
II	5(25%)	5(25%)	0.343
III	9(45%)	5(25%)	
IV	6(30%)	10(50%)	
After one week	n=19	n=20	
I	2(10.53%)	10(50%)	0.036*
II	9(47.37%)	7(35%)	
III	6(31.58%)	3(15%)	
IV	2(10.53%)	0(0%)	
After one month	n=16	n=18	
I	8(50%)	17(94.44%)	0.003**
II	8(50%)	1(5.56%)	
Outcome			
After one week	n=20	n=20	
Alive	19(95%)	20(100%)	0.311
Death	1(5%)	0(0%)	
After one month	n=16	n=18	
Alive	16(80%)	18(90%)	0.376
Death	4(20%)	2(10%)	

* P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).

CK-MB values ranged from 1.5 to 90 ng/ml, with a median of 35.58 ng/ml. Group 1 had a median of 34.5 ng/ml, and Group 2 had a median of 37.75 ng/ml (P = 0.163), showing no statistical significance. A week later, with 39 participants, CK-MB values varied from 1 to 37 ng/ml, and there were no significant differences between Group 1 and Group 2 (P = 0.866). After one month, with 34 participants, CK-MB ranged from 1.5 to 13 ng/ml (P = 0.534). Regarding Troponin values at diagnosis with 40 participants, the range was 0.09 to 2251.3 ng/ml (P = 0.978), with no significant difference between the groups. However, after one week (39 participants), Troponin showed a significant difference between the groups (P = 0.049*), ranging from 0.02 to 30 ng/ml. At one month (34 participants), Troponin also had a significant difference between the groups (P = 0.014*), ranging from 0.01 to 12 ng/ml. (**Table.3**).

Table 3. Comparison between the studied groups regarding the changes in cardiac enzymes along the study period

Variables	Group 1 (IVIG)	Group 2 (Steroid and IVIG)	P. value
CK-MB (ng/ml)			
At time of diagnosis	**n=20**	**n=20**	
Range	1.8 - 87	1.5 - 90	0.163
Median(Q1-Q3)	34.5(9.97-49.38)	37.75(26.32-83)	
After one week	**n=19**	**n=20**	
Range	1.5 - 37	1 - 17.8	0.866
Median(Q1-Q3)	7(3.7-12.8)	6.75(4.23-13)	
After one month	**n=16**	**n=18**	
Range	2.2-13	1.5 - 9	0.534
Median(Q1-Q3)	3.75(3.2-4.15)	4.15(3.03-4.78)	
Troponin (ng/ml)			
At time of diagnosis	**n=20**	**n=20**	
Range	0.15 - 295	0.09 - 2251.3	0.978
Median(Q1-Q3)	16.45(2.87-57.73)	14.1(5.23-84.58)	
After one week	**n=19**	**n=20**	
Range	0.02 - 30	0.03 - 1.2	**0.049***
Median(Q1-Q3)	1.3(0.17-10)	0.27(0.1-0.65)	
After one month	**n=16**	**n=18**	
Range	0.09 - 12	0.01 - 0.9	**0.014***
Median(Q1-Q3)	1.04(0.11-2.55)	0.18(0.02-0.3)	

* P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).

Concerning ECG findings, at diagnosis (40 participants), Regarding rhythm abnormalities, at diagnosis, 47.5% had an abnormal rhythm, with 40% in Group 1 and 55% in Group 2 (P = 0.342). One week later, 28.21% had an abnormal rhythm, significantly higher in Group 1 (47.37%) compared to Group 2 (10%) (P = 0.010*). After one month, the percentage decreased to 8.82%, with 18.75% in Group 1 and none in Group 2 showing abnormal rhythms (P = 0.054). For T-wave abnormalities at diagnosis, 67.5% had them, with no significant group differences (P = 0.311). One week later, 48.72% had T-wave abnormalities, and after one month, the percentage decreased to 14.71%, with no significant group differences (P = 0.421, P = 0.732, respectively). (**Table .4, Fig. 1**).

Table 4. Comparison between the studied groups regarding the change in ECG findings along study period

Rhythm	Total	Group (1) (IVIG)	Group(2) (Steroid and IVIG)	P. value
At time of diagnosis	**n=40**	**n=20**	**n=20**	
Normal	21(52.5%)	12(60%)	9(45%)	0.342
Abnormal	19(47.5%)	8(40%)	11(55%)	
After one week	**n=39**	**n=19**	**n=20**	
Normal	28(71.79%)	10(52.63%)	18(90%)	**0.010***
Abnormal	11(28.21%)	9(47.37%)	2(10%)	
After one month of diagnosis	**n=34**	**n=16**	**n=18**	
Normal	31(91.18%)	13(81.25%)	18(100%)	0.054
Abnormal	3(8.82%)	3(18.75%)	0(0%)	
T wave abnormalities	**Total**	**Group(1) (Steroid)**	**Group(2) (Steroid and IVIG)**	**P. value**
At time of diagnosis	**n=40**	**n=20**	**n=20**	
No	13(32.5%)	5(25%)	8(40%)	0.311
Yes	27(67.5%)	15(75%)	12(60%)	
After one week	**n=39**	**n=19**	**n=20**	
No	20(51.28%)	11(57.89%)	9(45%)	0.421
Yes	19(48.72%)	8(42.11%)	11(55%)	
After one month of diagnosis	**n=34**	**n=16**	**n=18**	
No	29(85.29%)	14(87.5%)	15(83.33%)	0.732
Yes	5(14.71%)	2(12.5%)	3(16.67%)	

* P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS).

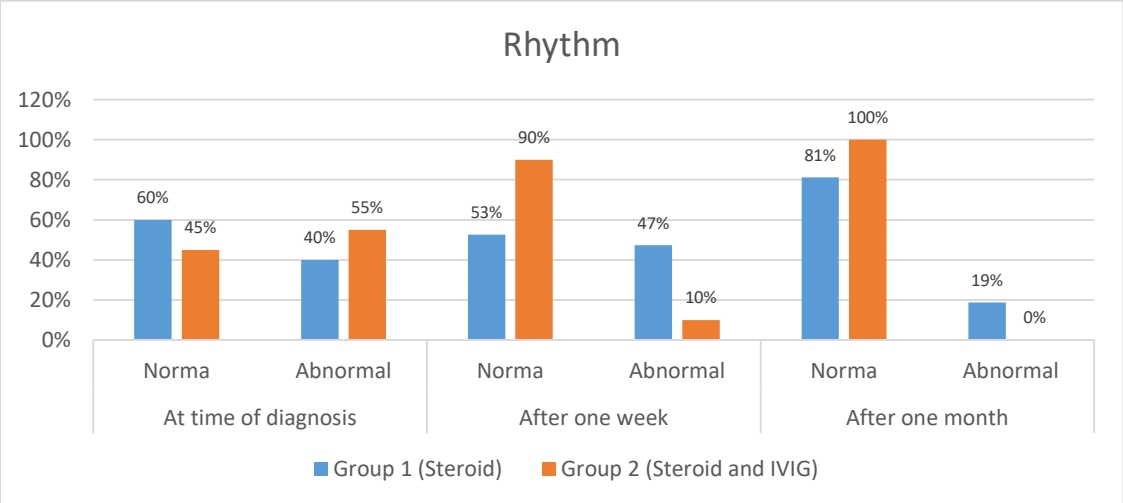

Fig. 1: Clustered column chart showing percentage of Rhythm distribution between the studied groups

Concerning Congenital Heart Disease (CHD), at diagnosis, 22.5% of participants had CHD, with 35% in Group 1 and 10% in Group 2 (P = 0.058). One week later, 20.51% had CHD, significantly higher in Group 1 (31.58%) compared to Group 2 (10%) (P = 0.095). After one month, 20.59% had CHD, with 31.25% in Group 1 and 11.11% in Group 2 (P = 0.147). Regarding Fraction Shortening, at diagnosis, the mean was 15.33±4.78, with no significant difference between groups (P = 0.694). One week later, the mean was 27.03±8.42, significantly higher in Group 2 (29.85±7.31) compared to Group 1 (24.05±8.65) (P = 0.041*). After one month, the mean was 33.68±5.32, significantly higher in Group 2 (35.83±3.76) compared to Group 1 (31.25±5.87) (P = 0.019*). Regarding Chamber Dilatation, at diagnosis, 87.5% had it, with no significant group differences (P = 0.633). One week later, 64.1% had chamber dilatation, with no significant group differences (P = 0.060). After one month, 47.06% had chamber dilatation, with no significant group differences (P = 0.089). Regarding Valvular Regurgitation, at diagnosis, 77.5% had it, with no significant group differences (P = 0.256). One week later, 61.54% had valvular regurgitation, significantly higher in Group 1 (78.95%) compared to Group 2 (45%) (P = 0.029*). After one month, 50% had valvular regurgitation, with no significant group differences (P = 0.169). Regarding Pulmonary Hypertension (PHTN), at diagnosis, 20% had it, with no significant group differences (P = 0.429). One week later, 12.82% had PHTN, with no significant group differences (P = 0.676). After one month, 5.88% had PHTN, with no significant group differences (P = 0.932). (**Table. 5**)

Table 5. Comparison between the studied groups regarding the changes in Echocardiographic findings along the study period:

Variables	Total	Group 1 (IVIG)	Group 2 (Steroid and IVIG)	P. value
CHD				
At time of diagnosis	**n=40**	**n=20**	**n=20**	
No	31(77.5%)	13(65%)	18(90%)	0.058
Yes	9(22.5%)	7(35%)	2(10%)	
After one week	**n=39**	**n=19**	**n=20**	
No	31(79.49%)	13(68.42%)	18(90%)	0.095
Yes	8(20.51%)	6(31.58%)	2(10%)	
After one month	**n=34**	**n=16**	**n=18**	
No	27(79.41%)	11(68.75%)	16(88.89%)	0.147
Yes	7(20.59%)	5(31.25%)	2(11.11%)	
Fraction shortening				
At time of diagnosis	**n=40**	**n=20**	**n=20**	
Range	6 - 22	6 - 21	6 - 22	
Mean±SD	15.33±4.78	14.9±5.17	15.75±4.45	
Median(Q1-Q3)	16(12-20)	16.5(9.25-20)	15.5(13-19.5)	0.694
After one week	**n=39**	**n=19**	**n=20**	
Range	10 - 41	10 - 40	13 - 41	
Mean±SD	27.03±8.42	24.05±8.65	29.85±7.31	
Median(Q1-Q3)	26(21-35)	22(17-29)	32(23.5-35)	**0.041***

After one month	**n=34**	**n=16**	**n=18**	
Range	22 - 41	22 - 41	28 - 40	
Mean±SD	33.68±5.32	31.25±5.87	35.83±3.76	
Median(Q1-Q3)	35(28-38)	28(28-37.75)	37.5(34.25-38)	**0.019***
Chamber dilatation				
At time of diagnosis	**n=40**	**n=20**	**n=20**	
No	5(12.5%)	3(15%)	2(10%)	0.633
Yes	35(87.5%)	17(85%)	18(90%)	
After one week	**n=39**	**n=19**	**n=20**	
No	14(35.9%)	4(21.05%)	10(50%)	0.060
Yes	25(64.1%)	15(78.95%)	10(50%)	
After one month	**n=34**	**n=16**	**n=18**	
No	18(52.94%)	6(37.5%)	12(66.67%)	0.089
Yes	16(47.06%)	10(62.5%)	6(33.33%)	
Valvular regurge				
At time of diagnosis	**n=40**	**n=20**	**n=20**	
No	9(22.5%)	6(30%)	3(15%)	0.256
Yes	31(77.5%)	14(70%)	17(85%)	
After one week	**n=39**	**n=19**	**n=20**	
No	15(38.46%)	4(21.05%)	11(55%)	**0.029***
Yes	24(61.54%)	15(78.95%)	9(45%)	
After one month	**n=34**	**n=16**	**n=18**	
No	17(50%)	6(37.5%)	11(61.11%)	0.169
Yes	17(50%)	10(62.5%)	7(38.89%)	
PHTN				
At time of diagnosis	**n=40**	**n=20**	**n=20**	
No	32(80%)	15(75%)	17(85%)	0.429
Yes	8(20%)	5(25%)	3(15%)	
After one week	**n=39**	**n=19**	**n=20**	
No	34(87.18%)	17(89.47%)	17(85%)	0.676
Yes	5(12.82%)	2(10.53%)	3(15%)	
After one month	**n=34**	**n=16**	**n=18**	
No	32(94.12%)	15(93.75%)	17(94.44%)	0.932
Yes	2(5.88%)	1(6.25%)	1(5.56%)	

* P-value >0.05: Non significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS). CHD: Congenital Heart Disease, PHTN: Pulmonary Hypertension

Discussion

In our study, the predominant findings include a median age of 2.1 years (range: 1 day - 11 years), with 70% of the cases being males and 80% originating from rural areas. Moreover, 70% of the cases have a low socioeconomic status, and 92.5% received care in the Pediatric Intensive Care Unit (PICU) while 7.5% were in the Neonatal Intensive Care Unit (NICU). This was consistent with **Shah et al., (2019) and Golpour et al., (2021)** who reported that myocarditis incidence is higher in males due to immune responses, hormonal factors, genetics, and lifestyle. Rural areas see more cases due to limited healthcare access, leading to delayed diagnosis. Low socioeconomic status contributes to disparities in healthcare access and living conditions. This was in

contrast to **Lin et al. (2019)**, who found no gender disparities but significant age differences in their contrasting our study, possibly due to different sampling techniques. **Yao and Zhan (2023)** meta-analysis on corticosteroids for pediatric myocarditis states that there was diverse age groups (mean/median ages: 2.2 to 7.5 years), suggesting broad consideration across ages.

In our study, Group 2 (IVIG combined with steroids) exhibited a statistically significant Troponin decrease compared to Group 1 (IVIG alone) after one week and one month. This was concordant with **Cole et al., (2019)** and **Bozdemir et al., (2022)** who found that IVIG's immunomodulatory properties reduce myocardial inflammation, reflected in lower Troponin levels. Adding steroids enhances anti-inflammatory effects, synergistically reducing inflammation and myocardial injury. Our results align with the research conducted by **Zhang et al. (2020),** showing that steroids decrease Troponin levels in myocarditis patients. Treatment within 24 hours resulted in a 32.4% , statistically significant reduction compared to later treatments (p-value=0.026).

Survival analysis in our study for Steroid alone and Steroid and IVIG groups found no statistically significant differences at one week or one month. This was consistent with **Schauer et al. (2021)** who reported a 92.5% transplant-free survival rate with IVIG and high-dose steroids, improving left ventricular systolic function. **Lin et al. (2019)** national retrospective study showed fewer deaths in the pediatric IVIG cohort compared to steroid-treated pediatric patients.

In our study, comparing Ross classification between IVIG alone and Steroid and IVIG groups showed significant differences. After one week, the Steroid and IVIG group had a significant increase in Ross Class I (50% vs. 10.53%, p = 0.036), and after one month, it had a significantly higher proportion of Ross Class I (94.44% vs. 50%, p = 0.003), indicating a more favorable outcome. This was in concordance with **Tymińska et al., (2022)** who mentioned that in myocarditis, immune dysfunction plays a key role, and immunotherapy with prednisolone mimics natural steroids, leading to milder cardiac damage and improved symptoms in the Steroid and IVIG group, suggesting a more favorable outcome. Also this was consistent with **Mille & Burstein, (2023)** who states that the Ross Classification grades acute myocarditis severity based on clinical presentation and heart dysfunction, with Class I representing a less severe stage. The Steroid and IVIG group exhibited a significant increase in Ross Class I compared to IVIG alone, attributed to the synergistic effects of IVIG moderating immune response and steroids suppressing inflammation.

Regarding ECG findings, T wave abnormalities at various time points were similar in both groups with no significant differences. Notably, the rhythm was significantly different after one week, with a higher proportion of normal rhythms in the Steroid and IVIG group. These findings suggest that Steroids following IVIG have a positive impact on restoring normal heart rhythms, indicating potential benefits for cardiac health and recovery, particularly in the short term. This was consistent with **Armbruster et al., (2022) who reported** reducing inflammation with steroids and IVIG in combination can help restore normal electrical conduction, improving ECG rhythms and aiding in the efficient restoration of normal heart activity, although **Peretto et al. (2019)** review associated steroids with improved arrhythmia management, suggesting potential enhancement of atrioventricular nodal

recovery. However, the long-term effectiveness of corticosteroids in this context remains uncertain.

In our study, fractional shortening measurements initially showed no significant differences between Group 1 (Steroid) and Group 2 (Steroid and IVIG) at diagnosis. However, after one week and one month, Group 2 displayed a statistically significant increase in fractional shortening compared to Group 1, our result align with research conducted with **Schauer et al. (2021)**, showing that the combination of IVIG and high-dose steroids was beneficial for improving left ventricular systolic function. Also align with **Schauer et al. (2023)** who reported substantial improvements in left ventricular function with high-dose steroids and immunoglobulin, with 70% achieving normalized ejection fraction within one year. **Huang et al. (2019)** focused solely on standalone IVIG treatment, excluding IVIG combined with steroids and found that IVIG's was effective in managing acute myocarditis with 1.73 times higher odds of left ventricular ejection fraction improvement (95% CI: 1.34 to 2.13).

Conclusion

Our study at Qena University Hospital highlights the potential of combining steroids with intravenous immunoglobulin (IVIG) in treating pediatric acute myocarditis. The combination therapy showed clear advantages, significantly reducing Troponin levels after one week and one month. Long-term improvement in Ross classification suggests more favorable outcomes. While radiological findings didn't differ significantly, substantial enhancement in ECG rhythms, particularly within the first week, indicates the treatment's potential in swiftly restoring normal heart rhythms. Overall, our findings underscore the effectiveness of IVIG and steroid combination therapy, offering a promising approach for managing acute myocarditis in pediatric patients.

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