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The New Era in the Surgical Management of Tetrology of Fallot in Pediatric Patients: A Meta-Analysis

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ABSTRACT

Background: Provided the high incidence of Tetrology of Fallot, a compelling need for different surgical management techniques have been raised. Thus, a new era was developed in this field that gave favorable results, however a debate still exists on the optimal technique to relieve the Right Ventricular Outflow Tract Obstruction that could lead to less mortality and morbidity, hence it was necessary to analyze data that compare these different techniques.

Moreover, there is a controversy between cardiac surgeons about the best technique to correct the RVOT in infants with Tetrology of fallot and so this study was done to compare between two frequent techniques according to their mortality and morbidity.

Aim of the work: Assess the outcome after surgical repair of tetrology of fallot in pediatric patients comparing between transannular patch and valve sparing techniques.

Methods: The present study was planned in accordance with current guidelines for performing comprehensive systemic reviews and meta-analysis including the PRISMA (Preferred Reporting Items For Systemic Review Meta-Analysis), MOOSE (Meta-analysis of Observational Studies in Epidemiology) and guidelines for randomized and nonrandomized studies.

In this study a meta-analysis was done to compare between the two most common techniques (21-32) that are used to relieve the RVOT that are Transannular patch VS Valve Sparing Repair the variable chosen include: Mortality the Indexed Right Ventricular Volumes, QRS duration, incidence of pulmonary regurgitation, Right ventricular Ejection Fraction, Left Ventricular Ejection Fraction and incidence of Reoperation. The principal summary measures were difference in means with 95% confidence interval and p value (to be of significant if $p < 0.005$) . The difference in means were combined across studies with MedCalc© version 15.8 (MedCalc© Software bvba, Ostend, Belgium.

Results: A total of 72 citation were identified of which 20 studies were potentially relevant and retrieved in full text only 12 studies fulfilled the eligibility criteria There was 74% of patients had a TAP and 26% of patients had VSR. Mortality was 291 among patients with patch repair and 104 among valve sparing repair. Reoperation was detected in 7 patients with TAP *VS* 6 patients in VSR. Occurrence of PR was detected in 14 patients in TAP *VS* 12 patients in VSR. The study detected favorable measures in Indexed right ventricular volumes, RV ejection fraction and QRS duration in patients with VSR than those with TAP. This study detected that both group of patients had approximately equal results of LV ejection fraction.

Conclusion: Our results reflected that Valve Sparing Repair for pediatric patients has better outcome in Mortality to relieve pulmonary stenosis, occurrence of pulmonary valve regurgitation as well as a less harmful effect on the right ventricular ejection fraction, better Indexed right ventricular volume and QRS duration than using transannular patching technique.

Both transannular patching and valve sparing repair have approximately the same effect on the left ventricular ejection fraction that may need further studies.

Keywords: Tetralogy of Fallot, Surgical Correction. Transannular patch, Valve Sparing Repair.

INTRODUCTION

Tetralogy of Fallot, one of the most common congenital anomalies of the heart consisted of right ventricular outflow tract obstruction (RVOTO), ventricular septal defect (VSD), aorta overriding and right ventricular hypertrophy, This combination of lesions occurs in 3 of every 10.000 live births, and account for 7-10 % of all congenital cardiac malformations. Patients are usually presented during neonatal period with cyanosis. The aetiology of Fallot's Tetralogy is multifactorial including untreated maternal DM, Phenylketonuria, and intake of retinoic acid. Its also associated with chromosomal abnormalities such trisome 21,18 and 13[(1)].

Risk of occurrence in families is 3% it can be easily diagnosed with Echocardiography that can give sufficient information for planning of surgical treatment [(2)].

On November 29,1945 Alfred Blalock performed the first systemic to pulmonary artery shunt procedure to palliate Tetralogy of Fallot in a child by increasing pulmonary blood flow it was named the Blalock-Taussing shunt (BT shunt) and this was the first truly successful palliation of

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congenital heart diseases and created an international sensation [3]. In 1946, Potts et al, described a descending aorta-to-pulmonary artery systemic to pulmonary artery shunt (Potts-Smith shun) [4].

In 1962, Waterston described an ascending aorta to pulmonary artery shunt. Potts-Smith and Waterston shunt procedures were technically easier to perform than classic BT shunting in small infants. However, both the Potts-Smith and Waterston shunts often resulted in excessive pulmonary blood flow, distortion of pulmonary artery, and problems during subsequent complete Tetralogy of Fallot repair. As consequences these two shunts are essentially no longer used [5].

In 1955, Kiklin performed the first successful repair of Fallot's Tetralogy with a pump oxygenator at Mayo clinic and this was the era of palliative surgical repair of Tetralogy of fallot [6]. The outcome of the surgical repair was excellent with minimal morbidity and mortality. To date, no difference in operative mortality and morbidity rates has been noted between transventricular and transatrial approaches for total correction [7].

Nowadays there are current trend for preservation of the pulmonary valve function (PVF) by different surgical strategies to avoid the deleterious consequences of severe PR and right ventricular (RV) dysfunction. These are including [8]:

1- Monocuspid trans-annular patch (Polytetrafluoroethylene {PTFE}, pericardial and contegra).
2- PV sparing (sub or supra-annular patch).
3- PA-RV conduit technique (contegra, homograft).

Contegra conduit has became popular due to its availability in all sizes and the acceptable results obtained an intermediate follow up especially in Tetralogy of Fallot with absent pulmonary valve, Pink Tetralogy of Fallot and Tetralogy of Fallot with multiple major Aorto-Pulmonary collaterals [9].

PA-RV Conduits used for congenital heart surgery (hompgraft or xenograft) in high risk tetralogy of fallot may suffer from degenertion and development of regurgitation, calcification and obstruction after implantation and may require replacement within 4-6 years, but recently Contegra was introduced for RVOT reconstruction with excellent follow up results [9].

METHODS

Data sources

The following databases were used until March 2017): MEDLINE; Cochrane Controlled Trials Register; Google Scholar, and Reference lists of relevant articles.

Search terms

The search was conducted using Medical Subjects Headings terms ("Tetrology of Fallot" or " Fallot's Tetrology " and " Rpaired tetrology of fallot with Transannular patching" or " Cardiac MRI to asses ventricular volumes after repair of TOF" or "Mortality after repair of TOF" or " Reoperation after TOF Repair"

Eligibility Criteria

Studies were considered if contain one or more of the following criteria:

1) Pediatric patients with repaired tetrology of fallot using transannular patching technique and/or valve sparing technique to repair RVOT.
2) Outcome studied Included any of the following:
   a- Indexed Right Ventricular Volumes assessed with cardiac MRI.
   b- Right Ventricular Ejection Fraction.
   c- QRS duration.
   d- LV EF.
3) Studies were prespective or Retrospective or nonrandomized or randomized observational studies.

Study selection

Steps that was done to select the studies:

1. Identification of titles of records through database searching
2. Removal of Duplication
3. Screening and selection of abstracts
4. Assessment for eligibility through full text articles
5. Final inclusion in study

Summary measures

The principal summary measures were difference in means with 95 % confidence interval and p value (considered statistically significant when $p < 0.05$)

Synthesis of results

Forest plots were generated for graphical presentation of clinical outcomes, and (I square) test for assessment of heterogenecity across the studies Each study was summarized by difference in standard deviation means for the results of the two techniques used in the repair

Risk of publication bias

Funnel plot was generated.

Statistics

Statistical analysis was done using MedCalc© version 15.8 (MedCalc© Software bvba, Ostend, Belgium).

Testing for Heterogeneity

Studies included in meta-analysis were tested for heterogeneity of the estimates using the following tests:

1. Cochran Q chi square test: A statistically significant test (p-value <0.1) denoted heterogeneity among the studies.
2. I-squared (I^2) index which is calculated as follows: $I^2 = \left(\frac{Q-df}{Q}\right) * 100\%$. The I-squared is interpreted as follows:

0% to 40%: might not be important

30% to 60%: may represent moderate heterogeneity

50% to 90%: may represent substantial heterogeneity

75% to 100%: considerable heterogeneity

Effect Size Estimation

Effect size for binary outcome measures was expressed as odds ratio (OR) with its 95% confidence limits (95% CI). For continuous outcome measures, effect size was expressed as standardized mean difference (SMD) and 95% CI of the SMD.

Pooling of Estimates

Estimates from included studies were pooled using both the Mantel-Haenszel fixed-effects method (FEM) and the DerSimonia Laird random-effects method (REM). In absence of significant heterogeneity, the FEM was considered; otherwise, the REM was considered.

Examination of Publication Bias

Publication bias was assessed by examination of Funnel plots**.**

A funnel plot is a plot of the estimated effect size (OR or SMD) on the horizontal axis versus the standard error (SE) for the effect size as a measure of study size on the vertical axis.

Large studies appear toward the top of the graph, and tend to cluster near the mean effect size. Smaller studies appear toward the bottom of the graph, and (since there is more sampling variation in effect size estimates in the smaller studies) will be dispersed across a range of values.

In the absence of publication bias the studies are expected to be distributed symmetrically about the combined effect size. By contrast, in the presence of bias, it is expected that the bottom of the plot would show a higher concentration of studies on one side of the mean than the other. This would reflect the fact that smaller studies (which appear toward the bottom) are more likely to be published if they have larger than average effects, which makes them more likely to meet the criterion for statistical significance.

Level of Significance

A two-sided p-value <.05 denoted statistical significance.

RESULTS

Table 1. Meta-analysis for the difference between VSR and TAP as regards IRVV

Study	VSR	TAP	Total	SMD	SE	95% CI	t- value	p- value
Cullen et al. 1995	11	13	24	-6.99	1.08	-9.236 to -4.742		
Davlouros et al. 2002	16	19	35	-0.81	0.35	-1.516 to -0.111		
Helbing et al. 1996	6	13	19	-0.63	0.48	-1.642 to 0.392		
Samyn et al. 2007	94	206	300	-0.37	0.13	-0.621 to -0.128		
Total (fixed effects)	127	251	378	-0.51	0.11	-0.732 to -0.285	-4.476	<.001
Total (random effects)								

Test for heterogeneity	
Cochran Q-value	37.755
DF	3
Significance level	p < .0001
I^2 (inconsistency)	92.05%
95% CI for I^2	82.85 to 96.32

SMD = standardized mean difference; SE = standard error; 95% CI = 95% confidence interval; DF = degrees of freedom.

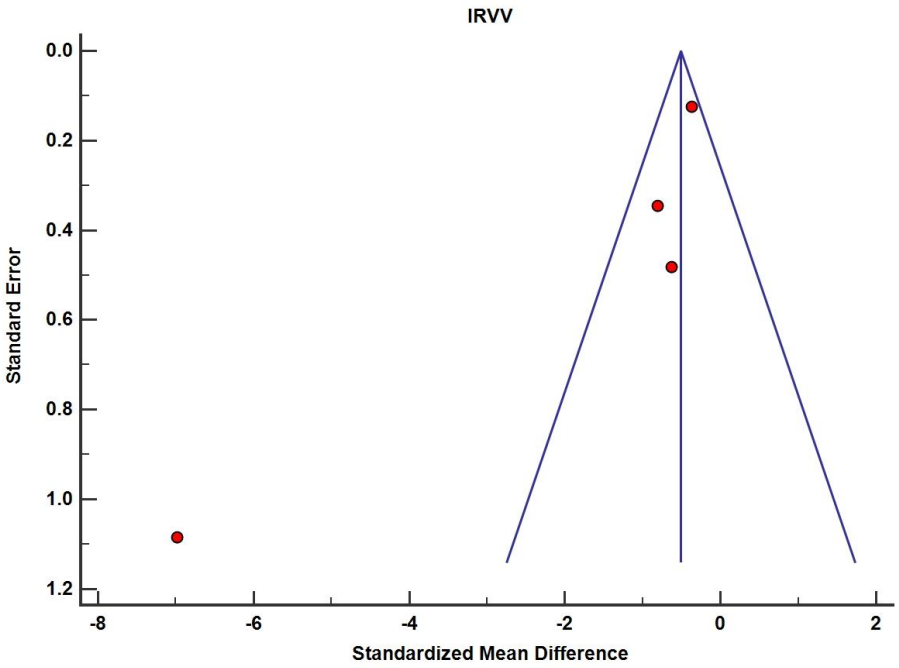

Figure 1. Funnel plot for the difference between VSR and TAP as regards IRVV

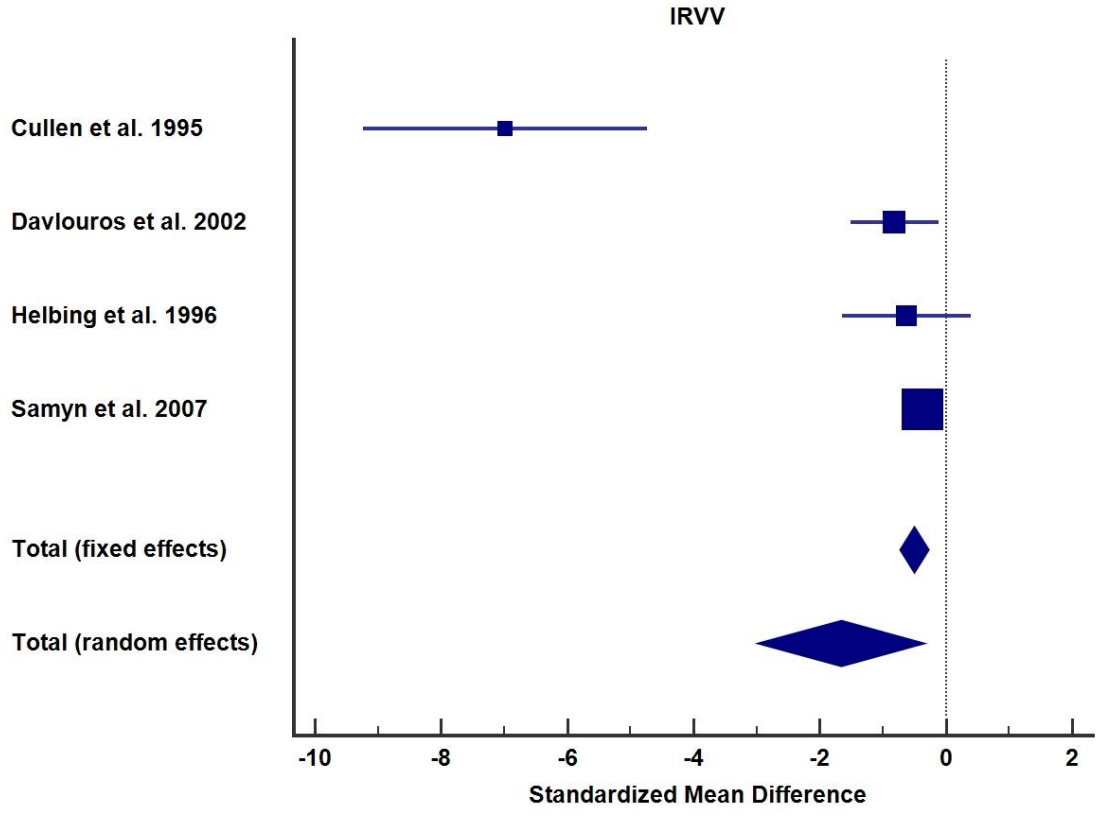

Figure 2: Forest plot for the difference between VSR and TAP as regards IRVV

Table 2. Meta-analysis for the difference between VSR and TAP as regards RVEF

Study	*VSR*	*TAP*	*Total*	*SMD*	*SE*	*95% CI*	*t-value*	*p-value*
Davlouros et al. 2002	16	19	35	0.689	0.342	-0.006 to 1.384		
Helbing et al. 1996	6	13	19	0.287	0.474	-0.713 to 1.286		
Samyn et al. 2007	94	206	300	-0.257	0.125	-0.502 to -0.012		
Total (fixed effects)	116	238	354	-0.121	0.114	-0.345 to 0.102	-1.066	.287
Total (random effects)	**116**	**238**	**354**	**0.175**	**0.339**	**-0.491 to 0.841**	**0.517**	**.605**

Test for heterogeneity	
Cochran Q-value	7.558
DF	2
Significance level	p = .023
I^2 (inconsistency)	73.54%
95% CI for I^2	11.37 to 92.10

SMD = standardized mean difference; SE = standard error; 95% CI = 95% confidence interval; DF = degrees of freedom.

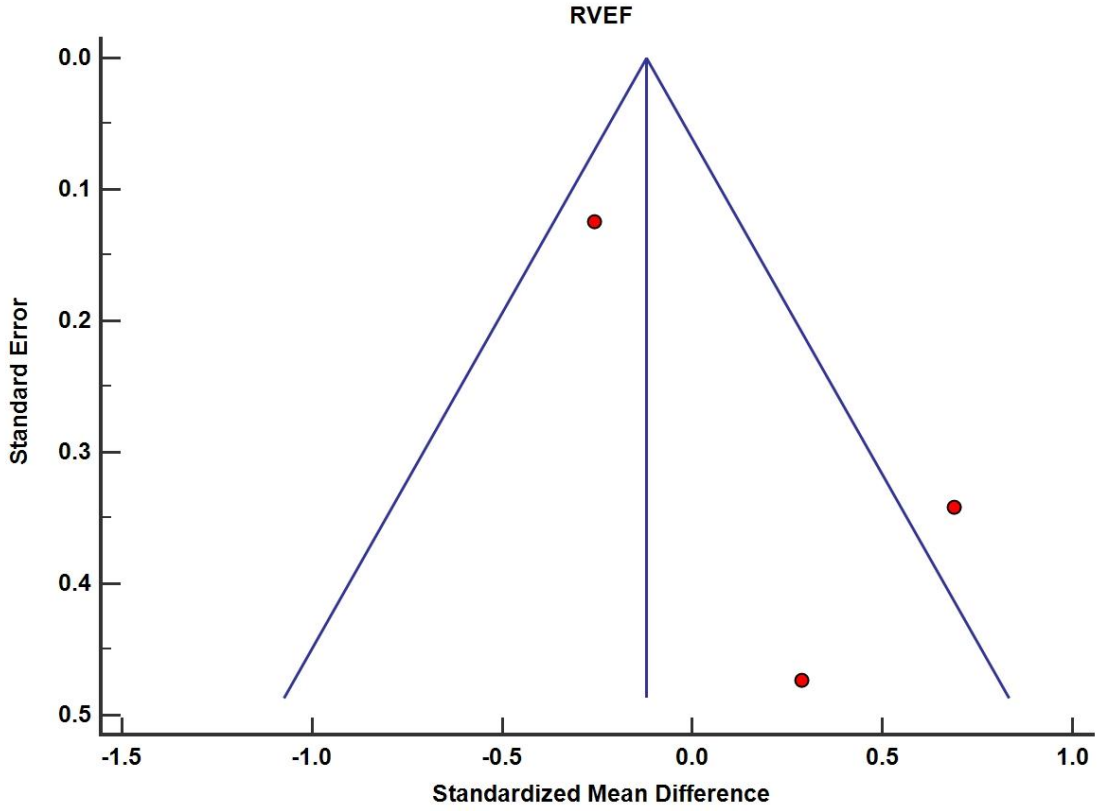

Figure 3. Funnel plot for the difference between VSR and TAP as regards RVEF.

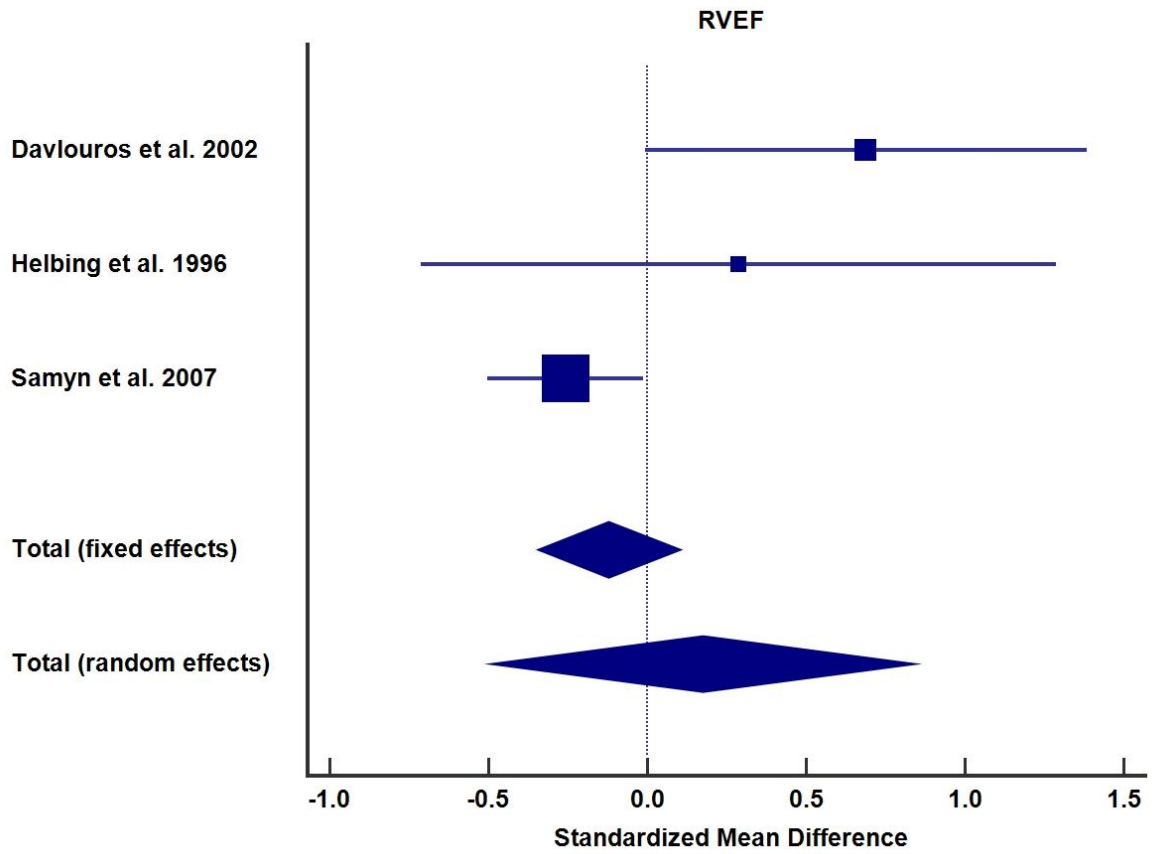

Figure 4. Forest plot for the difference between VSR and TAP as regards RVEF

Table 5. Meta-analysis for the difference between VSR and TAP as regards mortality

Study	*VSR*	*TAP*	*Odds ratio*	*95% CI*	*z-value*	*p-value*
Kirklin et al. 1989	40/559	51/255	0.308	0.198 to 0.481		
Lindberg et al. 2011	8/56	3/130	7.056	1.797 to 27.706		
Sarris et al. 2012	51/1525	230/2827	0.391	0.287 to 0.533		
Valente et al. 2013	5/136	7/442	2.372	0.740 to 7.598		
Total (fixed effects)	104/2276	291/3654	0.441	0.346 to 0.560	-6.688	<.001
Total (random effects)	**104/2276**	**291/3654**	**0.920**	**0.362 to 2.335**	**-0.176**	**.860**

Test for heterogeneity	
Q	26.882
DF	3
Significance level	p < .0001
I^2 (inconsistency)	88.84%
95% CI for I^2	74.06 to 95.20

DF = degrees of freedom.

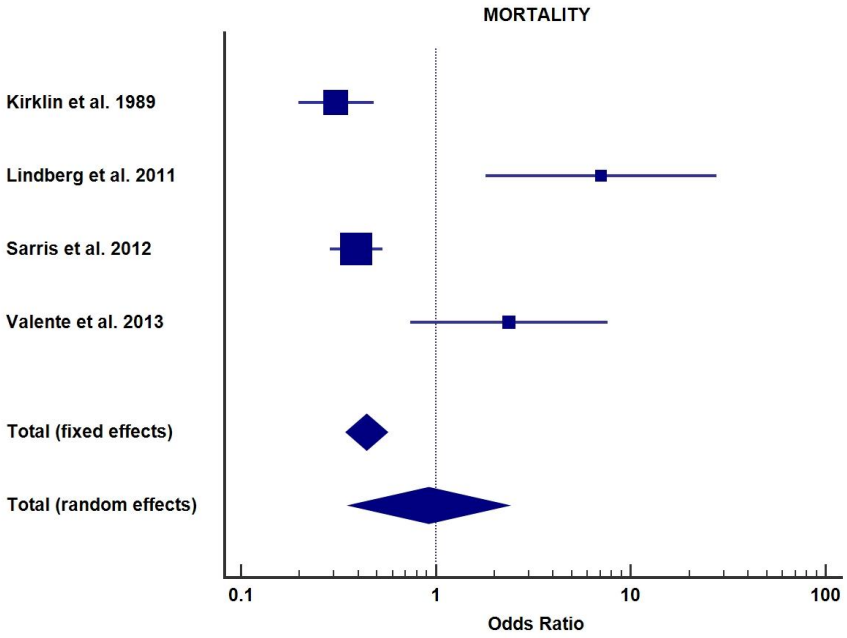

Figure 5 : Forest plot for the difference between VSR and TAP as regards mortality.

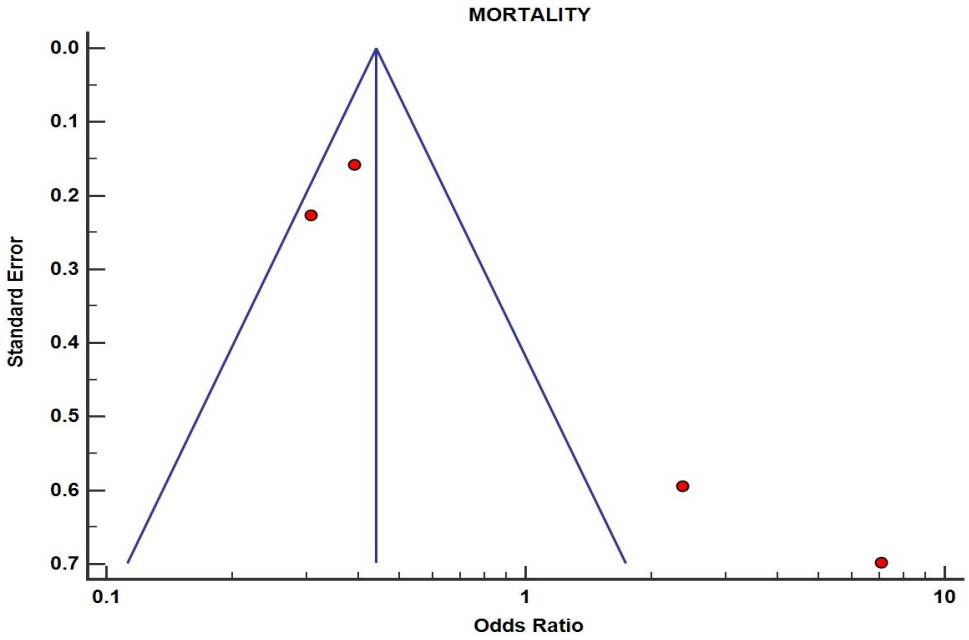

Figure 6: Funnel plot for the difference between VSR and TAP as regards mortality.

Table 6. Meta-analysis for the difference between VSR and TAP as regards reoperation

Study	*VSR*	*TAP*	*Odds ratio*	*95% CI*	*z-value*	*p-value*
Lindberg et al. 2011	1/52	0/130	7.054	0.283 to 175.852		
Meijboom et al. 1995	0/34	5/43	0.101	0.005 to 1.902		
Stewart et al. 2005	5/82	2/20	0.584	0.105 to 3.258		
Total (fixed effects)	**6/172**	**7/193**	**0.534**	**0.170 to 1.679**	**-1.074**	**.283**
Total (random effects)	6/172	7/193	0.667	0.090 to 4.962	-0.396	.692

Test for heterogeneity	
Q	3.718
DF	2
Significance level	p = .158
I^2 (inconsistency)	46.21%
95% CI for I^2	0.00 to 84.14

DF = degrees of freedom.

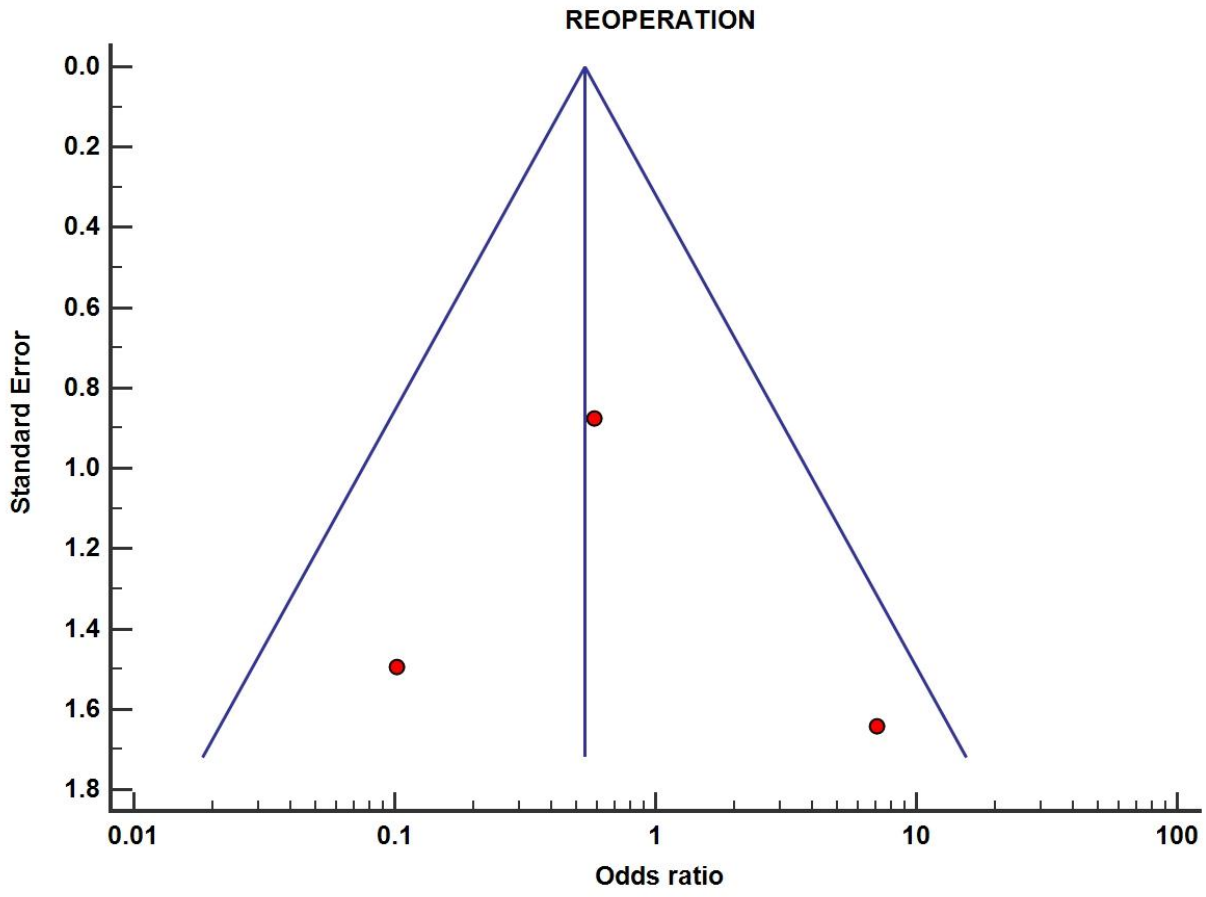

Figure 7 : Funnel plot for the difference between VSR and TAP as regards reoperation.

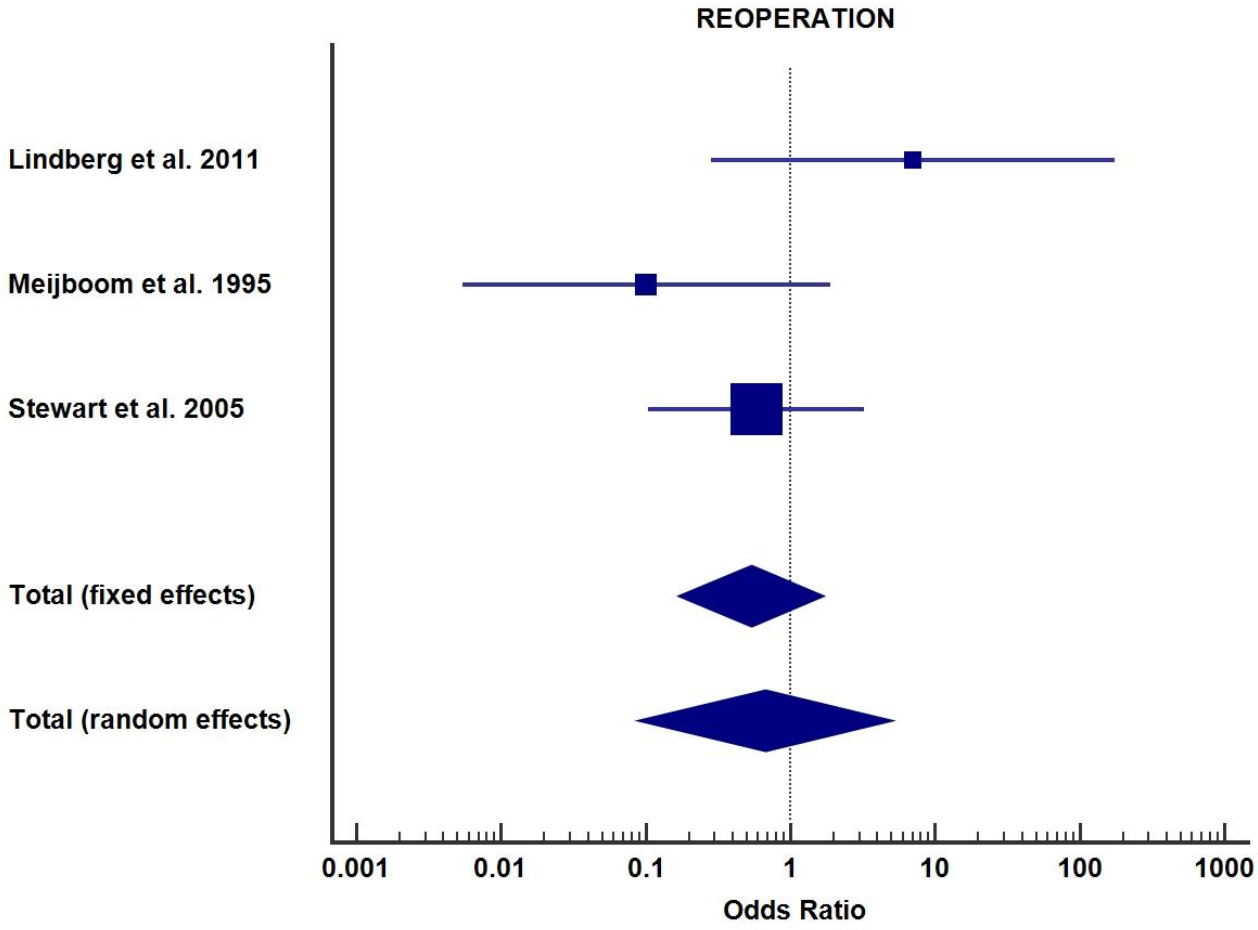

Figure 8 : Forest plot for the difference between VSR and TAP as regards reoperation.

DISCUSSION

Summary of evidence

It remains a surgical challenge to adequately relive RVOT in patients with tetralogy of Fallot without inducing significant pulmonary regurgitation and aiming for the optimal balance between the two.

Many publications support the complete primary repair of tetralogy of Fallot in infancy, even in neonates but concerns regarding possible increased mortality and morbidity for a very early repair has led surgeons to advocate a selective, non neonatal approach.

Controversery has continued over the indications for transannular patching as a part of repair tetralogy of fallot with pulmonary stenosis, because of insufficient information on potentially deteimental effect on the outcomes.

This systemic review meta-analysis was done to demonstrate the two popular surgical techniques for repairing the RVOT in pediatric patients who has total repair comparing two groups according to occurance of mortality and other post operative comblications.

Mortality: Some studies have shown that age at operation less than 6 months, low weight, and transannular patching of the RVOT is all associated with increased mortality after intracardiac repair.

The studies in the new era showed an excellent results regarding early mortality in patients with repaired tetralogy of Fallot despite earlier surgical repair and this due to improvement of the surgical skills and good protection of the myocardium during the procedure, so attention should be turned to detect late mortality and morbidity

Our systemic review meta-analysis collected the data only of the operative technique and we didn't take in consideration the exact age of the patients or their weight, it was found that mortality is more among infants who had repaired using the transannular patch than using valve sparing Repair.

Kirklin et al. [10] reported at his paper that transannular patching was a weak risk factor for death early postoperatively (30-day mortality) 4 %

used transannular patch and 1.5 % without, and not a risk factor for late death postoperatively including early death, 94% with transannular patch and 96.5 % without. Our study coincide with ***Sarris et al*** [11] which reported that regarding the types of procedures employed and their associated surgical mortality, ventriculotomy with transannular patching is associated with higher mortality than valve sparing repair. **Reoperation** Although we knew from several studies that correction of tetralogy of Fallot using transannular patching technique carries a higher risk of reoperation due to pulmonary regurgitation, this systemic review meta-analysis detected that there is no difference in reoperation between using Valve sparing repair and Transannular patching. ***Stewart et al.*** [12] studied 102 cosecutive patients with repaired tetralogy of Fallot 80 % of them was with valve sparing techniquws and 20 % with transannular path and there in no significant difference in the rate of reoperation between the two groups.

We supposed that our study depent on pooling of the results from different studies and these studies consider other causes for reoperation other than pulmonary regurgitation.

Kirklin et al. [11] reported that transannular patching clearly was a risk factor for reoperation for pulmonary regurgitation late postoperatively, that is not matching our study. ***Sarris et al*** [12] also reported that using transannular patching may be associated with higher incidence of reoperation due to pulmonary regurgitation. ***Lindberg et al*** [13] reported that the use of transannular patching was associated with a highly significant risk of reoperation.

Occurrence of pulmonary regurgitation

Our study demonstrated that using transannular patching was more common to cause PR when compared with Valve sparing repair and there is agreement among other papers in this concern especially when a large transannular patch was used ***Sarris et al.*** [12].

Stewart et al. [13] mentioned that a conscious effort has been made to avoid the use of transannular patching to preserve a functional pulmonary valve. That can be achieved by doing procedures that focus on the pulmonary annulus as much or more than preserving the valve cusps, this was done by using two patches above and below the annulus and it was preferable than a single patch crossing the annulus.

Indexed Right Ventricular Diastolic Volume It's a maesure that can be calculated by either using cardiac MRI or echorardiography it equal the value of Right Ventricular End Diastolic volume divided on Body Surface Area of the patients (RVEDV/BSA) and the value is ml/m2 and the noramal is 60-100 ml/m2. So papers that measure the RVEDV with no data about the BSA of the patients was excluded.

The advent of cardiovascular magnetic resonance (CMR) has allowed accurate and reproducible noninvasive measurements of biventricular size and function and quantification of valvular regurgitation.

This systemic review, meta-analysis showed that the IRVV is larger in patients had Transannular patching than Valve Sparing Repair. ***Saymn et al.***[14] studied 300 patients after examination with cardiac magnetic resonance imaging and concluded that patients with valve sparing techniques tended to have less pulmonary valve regurgitation, right ventricular enlargement and significantly higher right ventricular systolic pressure.

It seems that lower IRVV in patients with valve sparing techniques is due to less severe pulmonary regurgitation.

Right Ventricular Ejection Fraction Many studies reported the relation between the RV systolic function and the type of RVOT repair ***Saymn et al.***[14] ***and Davlouros et al.*** [15] and showed better RVEF with valve sparing techniques, owing these results to less incidence of pulmonary regurgitation.

Our systemic review and meta-analysis extended this positive relation between the technique of repair of RVOT and the systolic function of the right ventricle.

QRS duration there is a previous multicenter cohort study identified that QRS duration more than 180 ms as a predictor of death and clinical arrhythmia in patients with repaired tetralogy of Fallot. ***Norgard et al.*** [16] puplished a study that showed linear relationship between QRS duration in the resting ECG (prolongation is considered if more than 180 ms) and RV size that was higher in patients who were repaired with transannular patching technique. It was a highly sensitive predictor of symptomatic arrhythmia Analyzing the data extracted from the studies included in this systemic review it showed that the Valve Sparing Repair has a lower QRS duration than Transannular patching.

LIMITATIONS OF THE STUDY

* Studies that has been used in our systemic review were in English language only.
* Number of studies in the systemic review was small ranging from 2-4 studies for each outcome.
* Randomization and concealment were not clear in some studies
* At the last two decades of pediatric cardiac surgery using Transannular patching was the most common technique and the easiest for the surgeons

to do, so the number of patients who had Transannular patching are usually bigger than that of patients with Valve sparing repair.

* Term reoperation in some studies was found to include all events of reoperation either early post operative due to bleeding or in the perioperative period and the cause of reoperation was unclear in some studies.

* According to mortality some papers only include the hospital mortality and 30 days mortality but mortality after that was not documented.

RECOMMENDATIONS

We recommend the conduction of further studies that focus on using the new techniques that may decrease the incidence of reoperation due to occurrence of pulmonary regurgitation such implantation of various monocusp valves at repair of pulmonary stenosis (pericardial, allograft or polytetrafluoroethylene) as the long term effects of these efforts on the rates of reoperation is not proven at the time of doing this search.

CONCLUSION

Valve Sparing Repair for pediatric patients has better outcome in Mortality, to relieve pulmonary stenosis, occurrence of pulmonary valve regurgitation and also has less harmful effect on the right ventricular ejection fraction, Indexed right ventricular volume and QRS duration than using transannular patching technique.

Both transannular patching and valve sparing repair have approximately the same effect on the left ventricular ejection fraction that may need more further studies.

REFERENCES

1. **Kidd SA, Lancaster PAL *et al.*(1993):** The incidence of congenital heart defects in the first year of life. J Paediatr Child Health, 29:344-349.
2. **Blalock A, Taussing H B *et al.*(1984):** Landmark article may 19,1945:the surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia .By Alfred Blalock and Helen B. Taussing JAMA.,251(16);2123:38
3. **Potts WJ, Smith S, Gibson S *et al.*(1946):** Anastmosis of aorta to pulmonary artery, certain types in congenital heart diseases. JAM med Assoc., 132(11);627:31.
4. **Potts WJ, Smith S, Gibson S *et al.*(1946):** Anastmosis of aorta to pulmonary artery, certain types in congenital heart diseases. JAM med Assoc., 132(11);627:31.
5. **Ross RS, Taussing HB and Evans MH(1958):** Late haemodynamic complications of anastomoticsurgery for treatment of tetralogy of Fallot.Circulation, 18,553.
6. **Kirklin JW, Dushane JW, Patrick RT *et al.*(1955):** Intracardiac surgery with aid of a mechanical pump oxygenator system (gibben type) : report of eight cases,Proc staff meet Mayo clin., 30(10) :201-6.
7. **Pacifico AD, Kirklin JK, Colvin EV *et al.*(1990):** Transatrial-transpulmonary repair of Tetralogy of Fallot .semin thorac.cardiovasc.surg.,2 (1):76-82
8. **Vircella LA, Jacobs ML, Cameron DE(2013):** The birth of new era: the introduction of systemic to pulmonary artery shunt for treatment of cyanotic congenital heart diseases. Cardiol Young. , 23(26):852-7.
9. **Karl TR, Sano S Pornvilawan S, Mee R(1992):** Transatrial transpulmonaryrepair of tetralogy of fallot: favorable outcome of non-neonatal repair. Ann Thorac Surg., 54:903.
10. **Kirklin JK, Kirklin JW, Blackstone EH, Milan A, Pacifico A(1989):** Effect of transannular patching on the outcome after repair of tetralogy of Fallot. Ann Thorac Surg., 48: 783.
11. **Sarris G, Comas J, Tobota Z *et al.*(2012): Results of reparative surgery for tetralogy of fallot: data from the European association for cardiothoracic surgery congenital database** European Journal of Cardio-Thoracic Surgery, 42: 766-774.
12. **Stewart RD, Backer CL, Young L *et al.*(2005):** Tetralogy of fallot: Results of a pulmonary valve – sparing strategy.Ann thorac surg.,80:1431-8.
13. **Lindberg HL, Saatvedt K, Seem E, Hoel T, Birkeland S(2011):** Single-center 50 years' experience with surgical management of tetralogy of Fallot. Eur J Cardiothorac Surg ., 40:538–42.
14. **Saymn M, Andrew J, Ruchira G *et al.*(2007)::** Range of ventricular dimensions and function by steady state free precission cine RI in repaired tetralogy of fallot: Right ventricular outflow tract patch VS conduit Repair. Journal of magnetic resonance imaging ,26:934-940 .
15. **Davlouros PA, Kilner PJ, Hornung TS *et al.* (2002)*:*** right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. J Am Coll Cardiol ., 40*:* 2044–2052.
16. **Gunnar Norgard, Michael A. Gatzoulis, Fernando Moraes *et al.* (1996):** relationship between type of outflow tract repair and postoperative right ventricular diastolic physiology in tetralogy of fallot. Circulation AHA Journals , 94: 3276-3280.