COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

TREND, AND IMMEDIATE OUTCOMES OF TRANSCATHETER CLOSURE VERSUS SURGICAL LIGATION OF PDA IN CHILDREN WHO UNDERGONE CLOSURE OF PDA AT THE CARDIAC CENTER OF ETHIOPIA FROM 2012 TO 2022: COMPARATIVE CROSS-SECTIONAL STUDY.

BY: Dr. MOHAMMED NASIR (MD)

OCTOBER, 2023

HAWASSA, ETHIOPIA

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A THESIS TO BE SUBMITTED TO SCHOOL OF PUBLIC HEALTH HAWASSA UNIVERSITY COLLEGE OF MEDICINE AND HEALTH SCIENCES, IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR MASTER DEGREE OF PUBLIC HEALTH IN EPIDEMIOLOGY

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Approval Sheet

HAWASSA UNIVERSITY

SCHOOL OF GRADUATE STUDIES

EXAMINERS APPROVAL SHEET

We, the undersigned, members of the Board of Examiners of the final open defense by **Dr. Mohammed Nasir** have read and evaluated his thesis entitled " Trend, and Immediate Outcomes of Transcatheter Closure Versus Surgical Ligation of PDA in Children Who Undergone Closure of PDA at Cardiac Center of Ethiopia from 2012 to 2022: Comparative Cross-Sectional Study, Addis Ababa, Ethiopiaand examined the candidate. This is, therefore, to certify that the thesis has been accepted in partial fulfillment of the requirements for the degree of Master of Public Health in Epidemiology.

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Final approval and acceptance of the thesis is contingent upon the submission of the final copy of the thesis to the School of Graduate Studies (SGS) through the Department/School Graduate Committee (DGC/SGC) of the candidate`s department.

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APPROVAL SHEET

By my signatures below,I endorse that this thesis document is submitted in partial fulfillment of the requirement for the degree of Masters in Public Health (MPH) with speculations in Epidemiology in the graduate program of Hawassa University, department/school of Public Health and has been carried out by Dr. Mohammed Nasir (ID No: GPPHEpW/0011/13) under my supervision.

Therefore, I recommend the student fulfill the requirements and hence, hereby submit the thesis to the department.

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Annex-III: Declaration

I the undersigned, declare that this thesis my original work, has not been presented for a degree in only another university and that all sources of materials used for the thesis have been duly acknowledged.

Name: ***Dr. Mohammed Nasir***

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Date of submission: _____

This thesis has been submitted with my approval as university advisor.

Name: ***Fanuel Belayneh***

Signature: _____

Date: _____

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Acronyms

CCE-Cardiac Center of Ethiopia

IPTW-Inverse Probability of Treatment Weighting

ICU-Intensive Care Unit

PDA-Patent Ductus Arteriosus

SL-Surgical Ligation

TC-Transcatheter Closure

Abstract

Background: The Ductus arteriosus is an important fetal structure that helps in reducing right ventricular afterload during fetal life, but the patent ductus arteriosus (PDA) often closes spontaneously after birth. To prevent complications from patent ductus arteriosus, transcatheter closure (TC)and surgical ligation (SL) are management options for PDA that have not spontaneously closed. TC is preferred nowadays in older children and adults and SL in infants. However, the magnitude of the complications and outcomes associated with transcatheter closure (TC) and surgical ligation (SL) of PDA vary across studies. In this study, the trend, and immediate outcomes of TC of PDA versus SL of PDA were compared.

Methodology: This study was conducted on children under 18 years ofage who underwent TC and SL of PDA at a cardiac center in Ethiopia (CCE) from January1, 2013, to January1, 2022, by retrospectively reviewingtherecords from February 1, 2022, to June 1, 2022.664 patients who underwent PDA closure, (n=316) in theTCgroup and (n=348) patients in the SL group were included in this study.Trend analysis was performed using theCochrane-Armitage test to test for linear trends. The propensity scoresmultivariable logistic regression model used in the mainanalysis considered the following variables:EchocardiographicPDAsize, age at diagnosis, age at surgery,gender, weight at surgery, height at surgery, and presence of severe pulmonary hypertension. Usingthe inverse probability of treatment weighting (IPTW) by propensity score and after adjusting for baseline variables, the Man U test, chi-square test, and Fisher's exact test were used to compare the complications and outcomes of SL and TC of PDA.

Results: There was a linear trend in both transcatheter closure and surgical ligation of PDA. The SC-group patients were younger, lighter, and shorter and more proportion of patients had severe pulmonary hypertensionOverall complications were significantly higher with PDA surgical ligation compared with transcatheter closure ((112 (35.4%vs286 (71.9%)), p-value = 0.001)). Total mechanical ventilationtime, ICU stay, and hospital stay were higher in the surgical ligationgroup with ap-value of 0.001 each.

Conclusion: Transcatheter closure of PDA is a good and safe alternative to surgical ligation of PDA with reduced overall complication and shorter mechanical ventilation time, lower ICU stay, and lower hospital stay.

Keywords: PDA, surgical ligation of PDA, Transcatheter closure of PDA, comparative study

1. Introduction

1.1.Background

Ductus arteriosusis an important fetal structure that developed from the sixth left embryonic arch and serves as a passage between the left pulmonary artery and the aortic arch to relieve the right ventricle's afterload during fetal life(1).Its birth prevalence ranges from 0.87 to 1 per 1,000 live births and accounts for 10% of congenital cardiac disease(1–3).In normal-term babies, spontaneous closure of ductus arteriosus was anticipated to occur within 48 hours in 90% of cases and within 72 hours in 100% of instances(4).

Depending mainly on its size, the ductus arteriosus may persist even into later childhood or into adulthood due to the need for numerous factors in its spontaneous closure (4).Patent ductus arteriosus (PDA) if it is hemodynamically significant, can lead to several complications, such as heart failure brought on by increased pulmonary over circulation, aneurysmal dilatation of PDA with a risk of rupture, and in the long-term pulmonary obstructive illness (Eisenmenger syndrome). Infective endarteritis may also occur as a complication of small PDA(5,6).There are hence indications for PDA closure before the onset of the aforementioned complications. The indications are the presence of symptoms and left heart chamber dilatation regardless of the presence of symptoms(6)**.**

The two management options for PDA are transcatheter closure (TC) and surgical ligation (SL). Even though both management options had complications and variations in outcomes across centers, transcatheter closure(TC) of PDA is on the rise in the developed world while surgical ligation(SL) is on the decline(6,7).The aforementioned increased trend in TC wasidentifiedin a few studies that were done forinfants in developed countries(8–10).

Regarding developing countries, where closure is typically carried out in late childhood and adolescence, there isn'tmuch researchdone to investigate the trend and comparison of complication and outcome of TL Vs SC. The few Studies done in Pakistan and Indonesia that compared the outcomedifference in patients who weremanaged with TCVsSL showed that TC has lower complication, mortality, and length of hospital stay(11,12).

But, as far as we are aware, there is no studydone in Africa that assessed the trend in TCandSC of PDA over time, furthermore, there is only one study in Africa, conducted in Nigeria in 28

samples, compared the effectiveness of SLVsTC of PDAand reported, the latter to be the safest method(13).

Therefore, the purpose of this study is to compare the trend and immediate outcomes of the two PDA closure options as well as to assess the trends of PDA closure in the cardiac center of Ethiopia.

1.2.Statement of the Problem

PDA accounts for 18.1% of congenital heart diseases in Ethiopia(14). TC closure and SL are the 2 options for management. TC closure of PDA is becoming more common in older children in industrialized countries as a result of safety, changes in management guidelines, advancements in device technology, increase in expertise, and funding, as well as the availability of equipment(1,15).In developing countries as well, TC of PDA is a good option for surgical closure(1).However, since interventional procedures are carried out in Africa with the assistance of partners in Europe and America; this may contribute to an unclear trend for TC of PDA in Africa(16).

PDA closure is mostly delayed in underdeveloped nations, in contrast to Europe and America, making assessing complications of management and its outcome very crucial(1,17). Nonetheless, no study has been conducted in Ethiopia that assesses the trend of PDA management. Furthermore, there is a dearth of information about the efficacy of TC vs.SL of PDA in Ethiopia as well as across Africa.Therefore, this study evaluated the trend of PDA closure in cardiac centers of Ethiopia as well as compared the difference in complication rate and outcomeof the two management options (TC vs. SL) in cardiac centers of Ethiopia.

1.3.Significance of the Study

The results of this study could be used to monitor changes in TC and SL of PDA, which would aid in making decisions about whether to pool resources and funds. The other significance is aiding in management selection and outcome comparison with other centers to enhance management quality.

2. Literature Review

2.1.Epidemiology and clinical significance of patent ductus arteriosus

Patent ductus arteriosus (PDA) is a vital fetal structure that originates distally from the origin of the left subclavian artery and functions as a means of communication between the descending aorta and the pulmonary artery to divert the majority of the right ventricular output away from the more resistive pulmonary vasculature. Even though its patency is maintained in utero by high levels of nitric oxide, PGE2, and low oxygen concentration in fetal blood, anatomic closure of PDA occurs a few weeks after delivery due to a reduction in circulating prostaglandins and blood pressure and a rise in the partial pressure of oxygen (5).

It accounts for 5–10% of congenital heart diseases in term neonates; its patency causes murmur, tachycardia, bounding pulse, and heart failure, and it may also be asymptomatic. To provide proper management, it is necessary to use clinical criteria and diagnostic modalities like echocardiography (1,18).

Management options

Even though a patient's small PDA has no symptoms, hemodynamically significant PDA may be associated with heart failure, infective endarteritis, aneurysmal formation, and Eisenmenger syndrome (1,19)**.**In light of this, ductus closure is extremely important for any child or adult showing symptoms of significant left-to-right shunting. In asymptomatic patients with significant left-to-right shunting that enlarges the left heart chambers, closure is indicated to lower the risk of complications in the future (6).

PDA closure options for children as well as adults include surgical ligation and the use of different devices via the trans-catheter route (6).

2.2.Trends of closure of PDA

Although surgical ligation of PDA resulted in a higher overall closure rate than device closure, it is now less commonly done due to its high risk of complications (4–6,20,21).In favor of this, both industrialized and developing countries are seeing a decline in surgical closure, according to studies from the USA and South Africa, respectively (4,7,22,23).

Noticing the pattern, Studies from Ireland and the UK indicate that surgical ligation is now more frequent in neonates and infants than transcatheter intervention is in older children (15).

Complications of PDA surgical ligation

The overall rate of PDA surgical ligation complications varied between studies. For instance, studies in the United States and the United Kingdom found that total complications were 14.8% and 20.5%, respectively, whereas studies in less developed nations like Nigeria and Indonesia found that complications might go as high as 21.4% and 43.3%(7,12,13,20,24).

According to studies, a lot of postoperative complications were identified post-PDA ligation. Studies from the US, Canada, Thailand, and China, for instance, have revealed postoperative complications such as bleeding and pneumothorax(25–28). Chylothorax has been documented in studies conducted in Canada, the UK, China, Brazil, and Nigeria(20,24,26,29–31). Infectionwas reported as a complication inStudies conducted in the USA, Thailand, Brazil, and the Philippines(6,7,27,31,32).Multiple reports of vocal cord paralysis following surgery have been made from the UK, Italy, USA, Poland, Norway, and Canada (7,25,32–36)Additionally, studies in Korea, Saudi Arabia, Egypt, and Ethiopiarevealed left ventricular dysfunction following PDA ligation(37–40).Studies in China, the United Kingdom, and Italy found pleural effusion as a complication. In a study from Brazil and Korea, systemic hypertension was reported (31)(41). Studies from the USA and Thailand noted diaphragmatic palsy (27,28,30–33,42).Research in the USA reported a rib fracture, another in the USA reported a foreign body in the tissues and the creation of a fistula, while a study in Turkey revealed LPA stenosis(7,32,43).

Complications of transcatheter closure

Studies have found a range of complications following Trans catheter closure of the patent ductus arteriosus: 0% in India,4.8% in Ethiopia, 5% in Egypt, and 33% in the USA(44–46)(47). Hemolysis, infective endocarditis, embolization of the device, stenosis of the descending aorta, and stenosis of the origin of the left pulmonary artery are among the complications associated with transcatheter closure of PDA that have been documented(48).These complications were shown by studies conducted in the United States, Korea, Pakistan, South Africa, Saudi Arabia, Egypt, and Iran (22,49–55).

Studies from Portugal, Korea, South Africa, and Egypt showed the embolization of the device, with embolization percentages of 0.5%, 0.9%, 4.8%, and 2% in Portugal, Korea, South Africa,

and Egypt respectively. This may obstruct the descending aorta and branch pulmonary arteries(45,49,56,57).

Isolated flow acceleration in the LPA after TC closure of PDA, in contrast to isolated RPA and MPA flow acceleration, is widespread and has been documented in numerous papers from Israel, the United States, and Egypt(45,46,58). According to research from Switzerland, 21% of PDA devices have RPA and LPA stenosis(59). Studies from South Africa, Saudi Arabia, and Egypt, respectively, demonstrated that, although it is rare, obstruction of RPA and MPA due to embolization of the device into RPA and MPA may occur (45,52,57). This was supported by only 2% and 3.1% of patients, respectively, in Pakistan and South Africa studies following the device, experienced isolated flow acceleration in the RPA stenosis(55,57).According to research from Saudi Arabia(7.4%), Sudan(0.7%), and Egypt(0.3%), descending aorta narrowing caused by a device's intrusion into the aorta is a reasonably frequent consequence compared to RPA and MPA stenosis(45,52,60).

Studies from Korea and India reported LV dysfunction following device closure. (61,62).The other complications in the Korean research that were mentioned included hemolysis and infective endocarditis(49).

Studies conducted in South Africa, Sudan, Nepal, Pakistan, and Saudi Arabia found that patients needed reintervention after device closure attempts(22,51,60,63).

2.3.Complications: SL Versus TC

According to numerous reports, the surgical ligation of PDA has more complications than transcatheter closure(6,13,28,30,31).The magnitude, however, varies between research. The UK, China, USA, and Nigeria each recorded 20.5%, 13.7%, 37%, 21.4%, and 4%, respectively. (6,13,20,24,28).Even though there are fewer complications associated with transcatheter closure of PDA, there are still some, with overall complications of 1.8%, 1.4%, 8.5%, 33%, 48.7%, 7.8%, and 5% documented in studies from Portugal, China, Korea, the United States, Iran, Pakistan, and Egypt (28,45,46,49,54–56).However, a few studies, including those conducted in Iran, India, and Bolivia, did not identify any complications with device closure

(44,64,65).Contrarily, a single US study found that device closure had a higher rate of complications than surgery(8).

Comparative studies carried out in China and Nigeria revealed that surgical ligation and device closure, respectively, had complication rates of 13.7% versus 1.4% and 21.4 versus 3.57%(13,28).Research conducted in Indonesia, however, found no statistically significant difference in the number of complications between TC and surgical ligation(12).

According to studies conducted in Canada and Brazil, systemic hypertension developed in 4.7% and 69% of patients after surgical ligation, respectively(31,66).In Brazilian comparative research, no patients had systemic hypertension after device closure, however, a Nigerian study found that 6.3% of patients did (13,31).

After PDA ligation, LV dysfunction was seen in 42.86% of Ethiopian patients (37,39,67,68)Studies conducted in Egypt, Canada, Saudi Arabia, and the United States revealed a substantial number of patients developing LV dysfunction provided support for this. A study in India found that 25% of patients experienced LV dysfunction following device closure (62).A study carried out in Korea backed up this(61). Pericardial effusion was listed as a surgical ligation complication in studies conducted in the UK Ireland, and Finland with an incidence of 0.3% and 1% of patients, respectively(69,70).

In a Brazilian comparative study, patients with surgical ligation required more opioids than those with transcatheter closure(31).

2.4.Comparison of transcatheter closure with surgery by hospital stays

Studies from the USA, Brazil, and Sudan revealed that patients who underwent surgical ligation experienced longer hospital stays and stays in the intensive care unit (31,60,71).Specifically, the longer duration of hospital stays was corroborated by a meta-analysis conducted in China and individual studies conducted in Indonesia and Pakistan (12)(11,72).

Different studies have found different magnitudes of residual shunt after transcatheter closure of PDA versus surgery.For instance, different residual shunt reports have been found in studies after surgery, including 3.9% in Turkey, 6.7% in Nigeria, and 12% in another Nigeria study. Residual flow is a concern for device closure and similarly magnitude differs across studies 70% in the USA study, Indonesia at 2.7%, south Africa 3%% Bolivia at 0%(57,65,73–75).

According to a comparative study conducted in China, there are no differences in the residual shunt magnitude between surgical closure of PDA and device closure(30).This is refuted by a similar comparative research conducted in the USA and China, the device group had a higher residual (8,28).Pakistani study showed higher residual in the surgical group(11).

Comparisons based on mortality vary between studies as well.In the Philippines, mortality after surgical ligation is 10%, 0.8% in Nepal, 0.2% in Pakistan, and none in Nigeria, for example(6,51,63,76).According to a study from Spain, the United States, Iran, and Pakistan, mortality was greater in the surgical group(12,64,71,77).Numerous reports from Pakistan, China, and Bolivia indicate no mortality difference between surgical ligation and device closure, indicating no mortality(11,28,78).

3. Objectives

3.1.General objective

To demonstrate trend of TC Vs SL, and to assess the immediate outcome of TC and SL of PDA in children who undergone PDA closure in cardiac center of Ethiopia from 2012 to 2022.

3.2.Specific objectives

To demonstrate the trend of TC Vs SL of PDA in children who undergone PDA closure in cardiac center of Ethiopia from 2012 to 2022.

To compare immediate outcomes of TC Vs SL of PDA in children who undergone PDA closure in cardiac center of Ethiopia from 2012 to 2022.

4. Methods and Materials

4.1.Study area and period

The Cardiac Center of Ethiopia (CCE) is located in Addis Ababa, the capital of Ethiopia. It has offered free care to cardiac patients ever since it was established in 2012. It also provides both adult and pediatric cardiac surgeries as well as both adult and pediatric interventional procedures. The facility has five wards with ten beds each, one OR, one CATH lab, and one ICU with five beds. At least 50 adult and child patients are seen daily in this facility's outpatient department. The facility performs three cardiac operations and three interventional procedures each week. The hospital currently has 20 nurses working there, along with four cardiac and cardiothoracic surgeons, three pediatric cardiologists, and two adult cardiologists. This study was carried out in CCE from February 1 2022 to June 1,2022.

4.2 Procedures

Transcatheter closure

Before transcatheter closure of the PDA, we obtained informed consent from the patient'sparents, administered a prophylactic dose of intravenous ceftriaxone, used transthoracic echocardiography to confirm the diagnosis of PDA, and ruled out other associatedcongenital heartdiseases and used general anesthesia for sedation. In all of our patients, the transcatheter procedure began with the femoral artery and vein being punctured, a 5Fr. femoral sheath being inserted, and then heparin being administered. A 5Fr. MPA_2 catheter was inserted to measure the pressure in the right ventricle and pulmonary arteries.Aortography was performed after the descending aorta was catheterized with a 5 Fr. pigtail catheter. Images of the PDA were obtained using angiography using lateral and right lateral oblique views. The angiographic result guided the devicechoice in our setting. The delivery sheath was advanced using the femoral vein. In our center, ADO-1, ADO-2, Lifetech PDA device, Cocoon PDA device, PFM device, Amplatzer muscular VSD occluder, and coils were in use. Transthoracic echocardiography was performed to evaluate the remaining shunt after device deployment angiography.Following the procedure, the patient was monitored for complications for 12 hours in the hospital before receiving follow-up care two weeks later.

Surgical ligation

Likewise, before surgical ligation of PDA, we obtained informedconsentfrom the patient's parents, administered a prophylactic dose of intravenous ceftriaxone, and used transthoracic echocardiography to confirm the diagnosis of PDA, and to rule out other associated congenital heart defects,using general anesthesia for sedation in all cases. After that, based on the surgeon's preference and expertise, a posterolateral incision was made in the left chest,double ligation of PDA, or division and double ligation of PDA, or double ligation with clipping with metallic clip or clipping with metallic clip alonewere performed. Aprophylactic chest tube was inserted and the patients weremonitored for complications overnight and discharged the next day after being given an appointment after a week.

4.2.Study design

Comparative cross-sectional study

4.3.Source population

The source population consisted of all pediatric patients with PDA under the age of 18 who underwent TC or SLof PDA in the cardiac center of Ethiopia.

4.4.Study population

All PDA patients under the age of 18 who underwent PDA closure (TC or SL) in the cardiac center of Ethiopia between January 2012 and January 2022 were included in the study population.

4.5.Sample population

All PDA patients under the age of 18 who underwent PDA closure (TC or SL) in the cardiac center of Ethiopia between January 2012 and January 2022 were included in the study population and fulfill the inclusion criteria.

4.6.Inclusion and exclusion criteria

4.6.1. Inclusion criteria

All PDA patients under the age of 18 who had PDA closure (TC or SL) performed at the cardiac center in Ethiopia between January 2012 and January 2022.

4.6.2. Exclusion criteria

Syndromic patients, patients with additional congenital heart disease to PDA, and patients with incompletely documented patient outcomes were excluded from this study.

4.7.Sample size, sampling technique and sampling procedure

4.7.1. Sample size determination

All patients in the TC and SL group were included in the study, if they fulfill the inclusion criteria.

4.8.Study variables

4.8.1. Dependent variables

The trend of TC and SL of PDA

The difference in the complication rate of TC Vs SL of PDA

The difference in the outcome of TC Vs SL of PDA

4.8.2. Independent variable

PDA closure types (TC or SL)

4.8.3 Covariates

Age, sex, echocardiographic size of PDA, Angiographic size of PDA, severe pulmonary hypertension

4.9.Data collection procedure and tools

Data was collected for a period of 5 months. A structured questionnairewas used for data extraction. The questionnaire was adopted from the Society of Thoracic Surgeon version 3.1 form.

4.10. Data quality control

To ensure the internal validity (accuracy and precision) of the study, maximum effort was taken to assure the quality of data, to minimize errors and bias using the following measures, two days training for data collectors and supervisors was carried out to have a clear understanding about the objective of the study and data collection procedure.

The pre-testing of the structured format will be conducted on a 5% sample at Tasma Hospital (a private Hospital in Addis Ababa), who undergone PDA closure for PDA patients, before data

collection to assess the quality of the questionnaire. Process and structured format will be checked for completeness daily by immediate supervisors and the principal investigator. After checking for consistency and completeness, the supervisors submitted the filled questionnaire to the principal investigator who rechecked the questionnaire, to maintain the quality of data. Data was cleaned &and entered by the principal investigator and strict daily field supervision and spot-checking were carried out.

4.11. Data entry and analysis

The accuracy of the data was manually verified. The data was then cleansed and saved for consistency after being entered into the Epi info 7 program. The data was once again exported for analysis using SPSS version 28 and Microsoft Excel 13. After verifying the normality of continuous variables, appropriate descriptive statistics were performed. To verify normality, the Shapiro-Wilk test was applied.Categorical variables were described by frequency and percentage. The TC and SL groups have been analyzed for linear trends using the Cochrane Armitage test. Multivariable logistic regression was used to generate propensity scores based on the baseline characteristics of the patients in the SL and TC groups.The propensity scores multivariate logistic regression model used in the primary analyses considered the following variables: echocardiographic size of PDA, age at diagnosis, age at procedure, sex, weight at surgery, height at surgery, and presence of severe pulmonary hypertension.Using the inverse probability of treatment weighting (IPTW) by the propensity score and after adjusting for baseline variables, the Man U test, Chi-square test, and Fisher's exact test were used to compare complications and outcomes of TC and SL of PDA. The statistical significance was assessed using a 2-tailed p-value<0.05.

4.12. Operational definitions

The trend of PDA closure-change in TC or SL of PDA over time

Postoperative or postprocedural complications -the presence of any cardiac or extracardiac complicationspostoperatively or post-procedurein the hospital.

Small residual PDA-residual PDA of <1.5mm

Moderate residual PDA-residual PDA of 1.5-3mm

Large residual PDA-residual PDA of >3mm

Mild Left ventricular dysfunction- Left ventricular ejection fraction of 40-49%

Moderate left ventricular dysfunction- Left ventricular ejection fraction of 30-39%

Severe left ventricular dysfunction-Left ventricular ejection fraction of less than 30%

Small pericardial effusion-the maximum echo-free space between the heart and pericardium of <10mm in subcostal and apical four-chamber view

Moderate pericardial effusion-the maximum echo-free space between the heart and pericardium of 10-20mm in subcostal and apical four-chamber view

Large pericardial effusion-the maximum echo-free space between the heart and pericardium of greater than >20mm in subcostal and apical four-chamber view

Small pleural effusion-the maximum echo-free space between the lung and dome of diaphragm <10mm in subcostal view.

Moderate pleural effusion-the maximum echo-free space between the lung and dome of the diaphragm 10-20mm in the subcostal view

Large pleural effusion-the maximum echo-free space between the lung and dome of the diaphragm of greater than >20mm in subcostal view.

Flow acceleration in the aortic archleft pulmonary artery, and the right pulmonary artery- doppler velocity greater than 2m/s in the aortic arch,left pulmonary artery, and right pulmonary artery respectively.

Acute kidney injury-absolute increase in serum creatinine of 0.3mg/dl or a 1.5-fold increase in serum creatinine from the baseline.

Systemic hypertension-blood pressure that was at or above the 95^{th} percentile for children who are the same sex, age and height.

Pulmonary hypertension-measured in study by subtracting systolic gradient of PDA in CW from the systolic pressure of the patient to get the systolic pulmonary pressure.

Pulmonary hypertension crisis-in a patient who had/developed pulmonary hypertension later /postoperatively or post device closure) presented with tachycardia, hypotension, poor perfusion, altered mental status and enlarged liver.

Low cardiac output syndrome-patients who presented with altered mental status, cold extremity, tachycardia or bradycardia, hypotension, low urine output(<0.5ml/kg/hr.), and metabolic acidosis.

Hospital stays- measured in this study by the length of hospital stay, length of intensive care unit stays, length of stay in mechanical ventilation,

Immediate outcome-assessed by the presence or absence of complications, length of hospital stays, magnitudeof mortalityand the magnitude of residual PDA.

Mortality- death occurrence at any time before discharge from the hospital after post-surgery or post-procedure.

4.13. Ethical considerations

Before beginning the actual research, the ethical review committee and advisor gave their approval for the study. Hawassa University granted its ethical approval. The medical director of CCE was informed of the study's objectives and data from patient charts were extracted without using any personal identifiers to ensure confidentiality, and it was solely utilized for this study purpose.

4.14. Dissemination of the result

The result of this study will be presented and submitted in the form of soft and hard copy to Hawassa university, College of health science, department of public health. Presentation at professional, local, national and international meetings and publication in peer reviewed journals will be attempted for further utilization.

5. Results

5.1.Socio-demographic characteristics

The sociodemographic characteristics of both Groups, Group-TC, and Group-SL are presented in Table 1. In this study, 316 patients (47.6%) had TC, while 348 patients (52.4%) had SL of PDA. At the time of surgery, the median age for Group 1-TC was 3.8 (IQR: 1.6–5.6) and for Group 2-SC, it was 3 (IQR: 1.7–6; P = 0.15). Females made up 178(56.3%) in Group-TC and 213(61.8%) in Group-SL.Age at diagnosis, weight at surgery, and height at surgery, presence of severe PAH before surgeryshowedstatisticaldifferences between the two groups (TC and SC) with P values of 0.04, 0.02, 0.002, and 0.001 respectively.

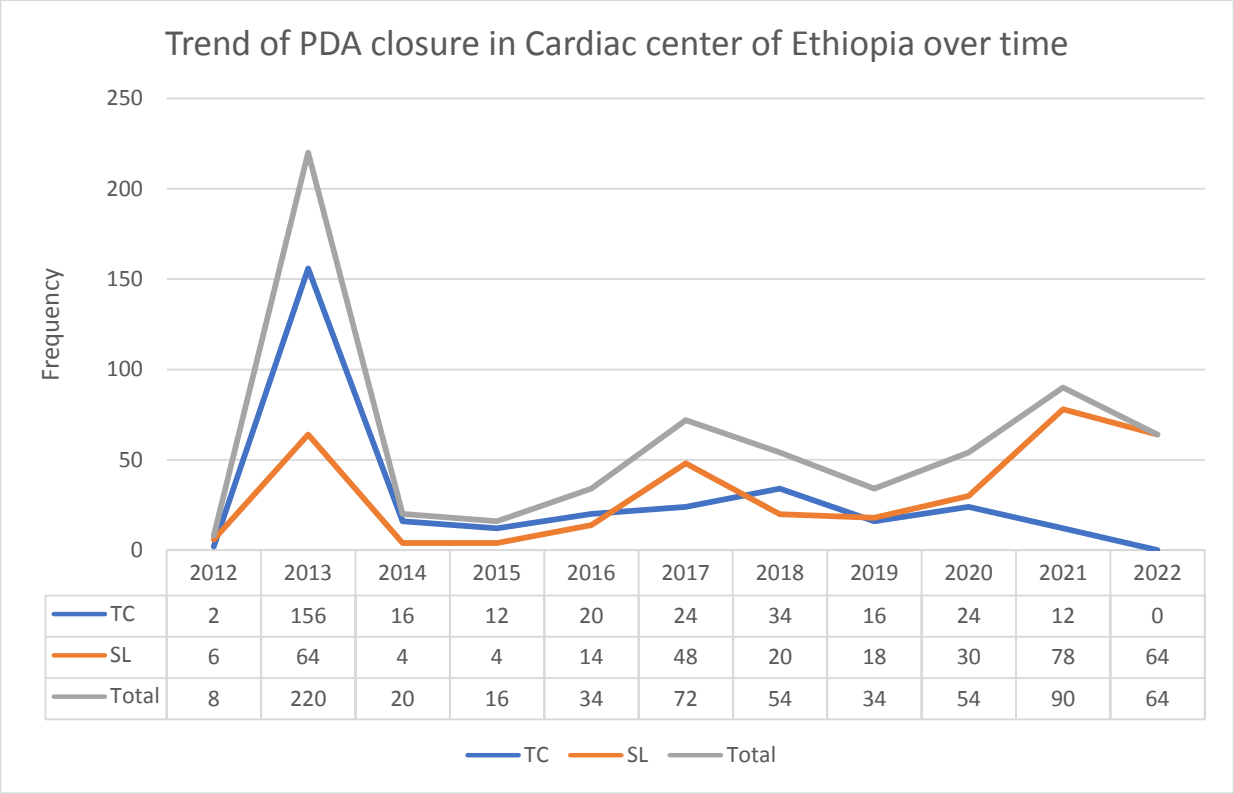
Table 1presentsthe sociodemographic and basic characteristics of patients who underwent PDA closure at the Cardiac Center of Ethiopia, 2012-2022, Hawassa, Ethiopia, 2023

Variables	TC 316 (47.6%)	SC 348 (52.4%)	P value
Age at diagnosis,median (IQR) (year)	3(1.6-5.6)	2.4(1-5)	0.04
Age at procedure, median (IQR)(year)	3.8(1.6- 6)	3(1.7-6)	0.15
Sex			0.20
Male n (%)	138(43.7)	135(38.8)	
Female n (%)	178(56.3)	213(61.8)	
Weight at surgery, median (IQR) (Kg)	12(10-16)	11(10-16)	0.02
Height at surgery, median (IQR)(cm)	100(92-107)	98(83-107)	0.002
Echocardiographic size of PDA, median (IQR) (mm)	5(4-8)	6(4-7)	0.06
Angiographic size of PDA, median (IQR)(mm)	4.5(3.5-7)	NA	-
Severe pulmonary hypertension			0.001
Yes n (%)	96(30.4)	184(52.9)	
No n (%)	220(69.6)	164(47.1)	

5.2.Trends of PDA closure

Figure 1shows trends of PDA closure over time. Cochran Armitage test was used to check if there is any linear trend for Group-TC and Group-SL and total procedure done over time and it showed that there was a linear trend in change in proportion of both Group-TC and Group-SC and total over time with P value 0.001 for both groups TC and SL and total procedures

done.2013 had the TC of PDA reach its highest point, and 2022 demonstrated its lowest. SL of PDA peaked in 2021, with 2013 and 2014 being the two years with the lowest values.



	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
TC	2	156	16	12	20	24	34	16	24	12	0
SL	6	64	4	4	14	48	20	18	30	78	64
Total	8	220	20	16	34	72	54	34	54	90	64

Figure 1Demonstrating trend of PDA closure over time in patients who have undergone PDA closure in the Cardiac Center of Ethiopia, 2012-2022.

5.3.Complications of PDA closure

Table 2demonstrates the two groups' percentages of various complications (SL group and TC group). Patients in Group SL had higher overall complications compared to Group TC. The SL group had a higher magnitude of all complications except flow acceleration in the RPA, LPA, and descending aorta. Encroachment of the device into the LPA and descending aorta caused flow acceleration in those vessels, whereas embolization of the device into the RPA caused flow acceleration in that vessel.

Table 2showsa comparison of complications of patients who underwent PDA closure in the cardiac center of Ethiopia, 2012-2022.

Complications	Group-TC 316(47.6%)	Group-SL348 (52.4%)	P value
Mild LV dysfunction	14(4.4)	34(9.8)	0.001
Moderate LV dysfunction	12(3.8)	18(5.2)	0.62
Severe LV dysfunction	2(0.6%)	6(1.7)	0.99
small residual PDA	34(10.8)	68(19.5)	0.01
Moderate residual PDA	4(1.3)	12(3.4)	0.02
small pericardial effusion	2(0.6)	8(2.3)	0.01
Moderate pericardial effusion	0(0)	2(0.6)	0.99
Moderate pleural effusion	0(0)	2(0.6)	0.99
Pneumothorax	2(0.6)	2(0.6)	0.34
Chylothorax	0(0)	4(1.1)	0.99
Hemothorax	0(0)	4(1.1)	0.99
Flow acceleration in the LPA	6(1.9)	4(1.1)	0.36
Flow acceleration in the RPA	6(1.9)	4(1.1)	0.03
Flow acceleration over the aortic arch	8(2.5)	4(1.1)	0.01
Ascending aorta to RPA fistula	0(0)	2(0.6)	0.99
Hypertension	6(1.9)	40(11.5)	0.001
Pulmonary hypertension crisis	0(0)	2(0.6)	0.99
Hyperkalemia	0(0)	2(0.6)	0.99
Hypokalemia	0(0)	8(2.3)	0.99
Hyperglycemia	0(0)	6(1.7)	0.98
Bleeding that needs a transfusion	7(2.2)	12(3.4)	0.13
Sepsis	0(0)	2(0.6)	0.99
Acute kidney injury	0(0)	8(2.3)	0.99
Metabolic acidosis	0(0)	10(2.9)	0.99
Metabolic alkalosis	0(0)	2(0.6)	0.99
Thrombocytopenia	0(0)	2(0.6)	0.99
Low cardiac output	0(0)	4(1.1)	0.99
Femoral pulse loss	2(0.6)	0(0)	0.99
Chest wall hematoma	0(0)	2(0.6)	0.99
Atelectasis	4(1.3)	8(2.3)	0.30
Paraplegia	0(0)	4(1.1)	0.98
One complication n (%)	72(37.3)	121(62.7)	0.001
Two complications	14(8.8)	50(79.4)	
Three or more complications	4(3.8)	19(82.6)	
Overall complication n (%)	112(35.4)	286(71.9)	0.001
Opioid use	3(0.94)	55(15.8)	0.001

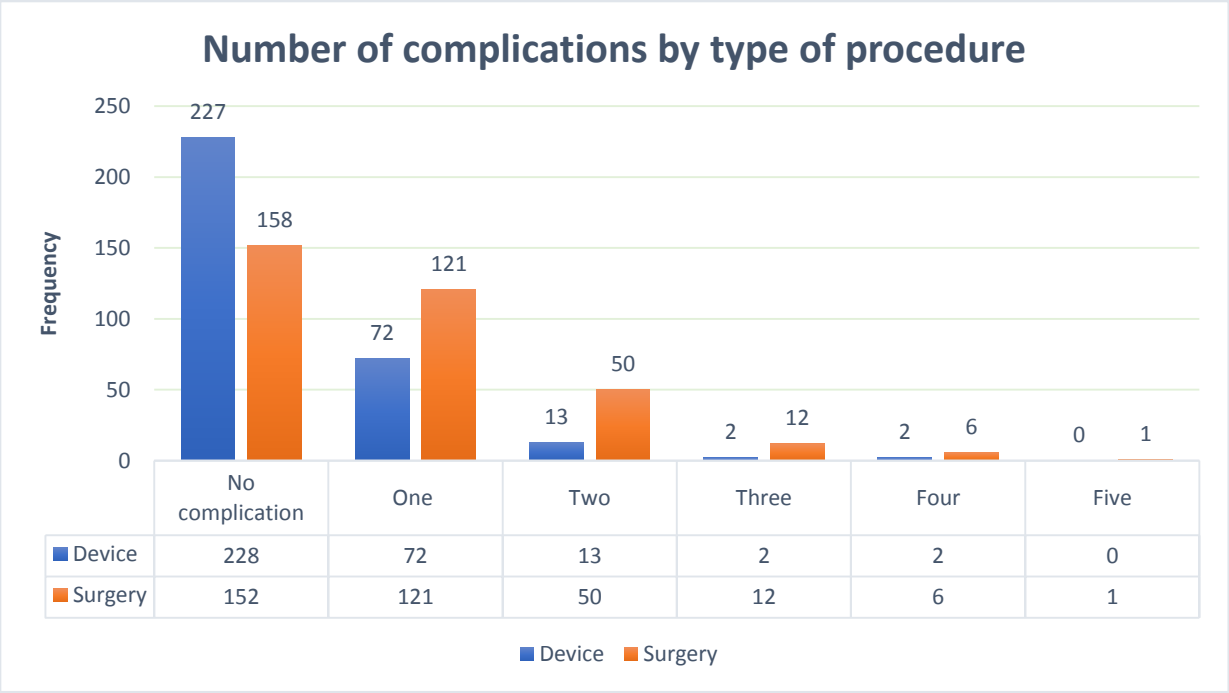


Figure 2Demonstrating the number of complications of TC and SL of PDA in patients who have undergone PDA closure in the Cardiac Center of Ethiopia, 2012-2022.

5.4.Outcome of PDA closure

Differences in total length of mechanical ventilation, length of ICU stay, and length of hospital stay were statistically significant between Group-TC and Group-SC patients, all stays were more in Group-SC patients. There was no significant difference in the proportion of reoperation and death between the two groupsTable 3.

Table 3presentsthe outcome of TC Vs SL in patients who have undergone PDA closure in the Cardiac Center of Ethiopia, 2012-2023.

Outcome	TC	SL	P value
Length of mechanical ventilation median (IQR)(hr.)	4(3-6.75)	9(4-13)	0.001
Length of ICU stay median (IQR)(days)	1(1-3)	3(1-5)	0.001
Length of hospital stay median (IQR)(days)	2(2-2.1)	4(2-6)	0.001
Failed device closure n (%)	6(1.9%)	-	-
Death n (%)	1(0.3)	0	0.99

6. Discussion

Our study compared the outcomes, magnitude of complications, and trend of SL and TC closure of PDAin a cardiac center inEthiopia. Our finding showed both SL and TC PDA showed a linear trend, and it was found as well that the SL group had statistically significantly greater percentages of overall complications, mild LV dysfunction, mild pericardial effusion,systemic hypertension, and a higher need foropioids as a complication.Regarding the outcome, our study also revealed that the SL group experienced milder and more moderate residual PDA and longer ICU and hospital stays.In addition, we reported ahigher percentage of flow acceleration in RPA and the descending aorta in the TC group.

Although the SL and TC of PDA show a linear trend, they have significantly decreased since 2014 as a result of insufficient device availability and the COVID-19 pandemic, which affects both the patient load and the availability of various equipment.

Similar studies from China, Brazil, and Nigeria corroborated the study's finding that there were more overall complications in the SL group compared to the TC group(13,28,31).Contrary to this, however, one study from the USA found that TC complications were higher than SL complications(8).Additionally, research from Indonesia revealed no differences in complications magnitudebetween the two groups(12).The age difference between study participants and the experience of professionals in various nations can both be used to explain the discrepancy in reporting the magnitude of complications between SL and TC.

The higher LV dysfunction percentage in SL found in our study is supported by a previous study that was carried out in Ethiopia, where 42.9% of patients experienced mild LV dysfunction after surgery, as opposed to studies done in Korea and India, where only 25% and 18.6% of patients experienced the same complication(40)(62)(61).The decrease in LV preload and rise in LV afterload following PDA ligation account for the decline in LV function. Because PDA causes a left-to-right shunt and increases LV preload after ligation, the LV preload decreases noticeably. The increase in afterload is caused by the fact that, before ligation, the LV pumps blood to both the high-resistant aorta and low-resistance pulmonary circulation. However, after closure, the LV only pumped blood against the high-resistance aorta.Further study is needed since it is unknown why surgical ligation causes LV dysfunction to develop more frequently than TC.

Only a few studies in device closure but none in surgical ligation demonstrated flow acceleration in the RPA. In comparison to studies conducted in Pakistan and South Africa, which revealed flow acceleration in the RPA of 2% and 3.1%, respectively, our study found a comparable figure (1.9%)(55)(57).Due to the RPA's anatomical distance from the PDA, the rarity of flow acceleration in RPA following surgical closure can be explained. Even though the RPA is anatomically far away from the PDA, it happens frequently during device closure that the device may embolize to the RPA.

Acceleration of blood flow in the descending aorta as a result of device embolization or encroachment of the device to the descending aorta, as in our study, has been documented in numerous studies. It has been reported in studies in the USA(1.9%) and (0.3%)(50), Saudi Arabia (7.4%), Sudan (0.7%), Egypt (0.3%), and in our study (2.5%)(45)(60)(52)(46). After surgical PDA ligation, there is a possible risk of inadvertent injury to the descending aorta (79). But reports are very rare.

Even though PDA is an extracardiac structure, there have been reports of pericardial injury and pericardial effusion in other studies, such as those conducted in the UK and Finland, with pericardial effusion proportions of 0.3% and 1%, respectively, which are lower than the 3.3% described in our study(70)(69).This variation in pericardial effusion prevalence following surgical PDA ligation can be attributed to the surgeon's experience. In our research, there were only 2 patients in the device group who experienced pericardial effusion; nevertheless, there have been no reports of pericardial effusion following device closure of PDA. This can be a result of the chest device technique not involving any external manipulation.

A study from Korea showed a significant number of patients developed systemic hypertension after PDA surgical ligation (41). Our report of 11.5% systemic hypertension following PDA ligation is higher than that reported from a study in Canada (4.7%) but lower than that from a study in Brazil (67%)(31,66).A possible cause is sympathetic nervous system hyperactivity, which led to a significant increase in catecholamines.There are limited reports of systemic hypertension following TC; one study from Nigeria found 6.3% of systemic hypertension following device closure, while Brazilian research did not find any cases of systemic hypertension(13)(31). Therefore, the manipulation of the aortic arch that enhances the

sympathetic surge is high in SL compared to TC, which can be used to explain why there is a higher prevalence of systemic hypertension following SL.

Comparable to our study, Patients in a Brazilian comparison study who underwent surgical ligation needed more opioids than those who underwent transcatheter closure(31).This can be explained by the fact that the expected pain score is high for surgical ligation because it is more invasive than TC.

Similar to a study conducted in Pakistan, our research found that the surgical group had more residual PDA than the TC group did (11). However, research from the USA and China disputes our findings(8)(28). Furthermore, in contrast to our data, another Chinese study found no variation in the magnitude of residual in the TC and SC(30). This discrepancy in residual PDA reporting may be caused by the fact that surgical expertise and interventional cardiology ability are the key determinants of residual PDA occurrence.

Studies from the United States, Brazil, Sudan, China, Indonesia, and Pakistan corroborated our study's findings that patients who underwent surgical ligation had longer hospital stays and stays in the intensive care unit(31,60)(71)(72)(11,12).The overall complications are more prevalent in SL of PDA than TC of PDA, which explains this.

Limitations of the study

This study has many limitations. The cross-sectional nature of the study design may lead to limitations in identifying complications associated with TC and SL closure of PDA that can be detected in the medium to long term, and its retrospective nature can lead to classification bias. Additionally, becausethiswas a single-centerstudy,generalizationscannotbemade. However, this study is important for improving the quality of TC and SL closure of PDA in Ethiopia because it providesimportant baseline data facilitatescomparison of the centers'results with those of other centers,and can help make management decisions(select TC or SL PDA for PDA closure) and helpestablish funding priorities and resource allocation during PDA closure.

7. Conclusion and recommendation

7.1.Conclusion

Even though the magnitude of TC and SL of PDA had a linear trend over time, both TC and SL of PDA have significantly decreased compared to their highest magnitude in 2013.

Because it has fewer overall complications, shorter hospital stays, fewer stays in the intensive care unit, fewer stays on mechanical ventilation, and last but not least, it is a non-invasive procedure, TC of PDA is a better option than SL of PDA.However, when doing TC of PDA, care should be taken to avoid complications in major vessels such as flow acceleration in the arch, LPA, RPA, and absence of a pulse in the femoral artery.

7.2.Recommendations

The following recommendations are made basedon the studyresults:

1. Increase the number of TC of PDA.
2. It is important to support skillsdevelopment programs for SLof PDA

Inaddition,the following topics should be further explored for research:

1. Investigate the long-term complications and outcomes of TC of PDA.
2. Factors affectingthe change in TC and SL of PDA trends over time.
3. Factors affectingcomplicationandoutcomeof TC and SL of PDA
4. Factors associatedwith each complicationTC or SL of PDA.
5. The association of TC of PDA with flow acceleration in the arch, LPA and RPA.
6. The risk factors for the disappearance of femoral pulse in TC of PDA.

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Annexes

Annex I: Questionnaire

Sociodemographic factors
A. Age at diagnosis…..
B. Age at procedure…..
C. Sex of the patient 1. male 2. female
Anthropometric characteristics of the patient
A. Weight at procedure…..
B. Height at procedure…..
Clinical characteristics of the patient
A. Echocardiographic size of PDA…..
B. Angiographic size of PDA…….
C. Severe pulmonary hypertension 1. Yes 2. No
Transcatheter/ surgical ligation of PDA and complications
A. Year of procedure…..
B. Type of intervention 1. Transcatheter closure 2. Surgical ligation
C. If the answer for B is 1, specify type of device…..
D. If the answer for B is 2, specify type of surgical ligation…..
E. Left ventricular dysfunction 1. Yes 2. No
F. If the answer for E is 1, specify type of left ventricular dysfunction…….
G. Pleural effusion 1. Yes 2. No
H. If the answer for H is 1, specify type of pleural effusion…….
I. Pneumothorax 1. Yes 2. No
J. Chylothorax 1. Yes 2. No
K. Hemothorax 1. Yes 2. No
L. Chest wall hematoma 1. Yes 2. No
M. Flow acceleration of aortic arch 1. Yes 2. No
N. Flow acceleration in the left pulmonary artery 1. Yes 2. No
O. Flow acceleration in the right pulmonary artery 1. Yes 2. No
P. Aorta to right pulmonary artery fistula 1. Yes 2. No
Q. Femoral pulse loss 1. Yes 2. No
R. Systemic hypertension 1. Yes 2. No
S. Pulmonary hypertension crisis 1. Yes 2. No
T. Low cardiac output syndrome 1. Yes 2. No
U. Electrolyte imbalance 1. Yes 2. No
V. If the answer for U is 1, specify type of electrolyte imbalance…….
W. Metabolic complication 1. Yes 2. No
X. Hematologic complication 1. Yes 2. No
Y. If the answer for X is 1 specify the hematologic complication……
Z. Sepsis 1. Yes 2. No
AA. Acute kidney injury 1. Yes 2. No
BB. Residual PDA 1. Yes 2. No
CC. If the answer for BB is 1, mention the size of residual PDA in mm…….
DD. Death 1. Yes 2. No

EE.	Length of hospital stay in days…….
FF.	Length of ICU stay in days……...
GG.	Length of mechanical ventilation in hours ……...