

Original Article: Comparison of the Therapeutic effect of Thrombolytic Drugs with Surgical Procedures in Right Atrial Thrombosis

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ABSTRACT

Objective: Cardiac thromboses are not uncommon, but right atrial thromboses are extremely rare. **Methods:** This study is a systematic study. 1541 articles were analyzed based on keywords and according to pubmed, scopus, web of science and embase databases. After removing duplicates, 964 articles remained. Finally, after reviewing the articles according to the title and abstract, 906 articles were removed and only 58 articles were included in the study and analyzed. **Results:** After the investigations, the results showed that in the studies, surgical treatments and anticoagulation and thrombolysis treatments were used to treat patients. **Discussion:** Finally, according to the data obtained from this study, it has been shown that the use of anticoagulation and thrombolysis treatment methods compared to surgical treatment for the treatment of patients can be associated with fewer complications for them. The use of surgery as the first treatment option can be combined with the use of antibiotics to prevent infection in patients. Therefore, the type of treatment can be chosen based on the clinical process and clinical symptoms of the patients.

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Introduction

Cardiac thromboses are not uncommon, but right atrial thromboses are exceedingly rare. Thrombosis in general can cause various complications such as systemic embolism and pulmonary embolism [1-3]. Right atrial thrombi can be formed primarily in the right atrium or secondary to thrombi caused by peripheral veins, and according to the size and spread of the thrombus, they can range from asymptomatic cases to massive pulmonary embolism and even death. Right atrial thrombi include two different types, the first type includes non-fixed and mobile thrombi that are thromboembolic in nature and form in the atrium with a normal structure. The second type of thrombi attached to the wall of the atrium, which are formed inside the atrium with an abnormal structure or the presence of foreign objects such as catheters [4-6]. Different risk factors in the development of right atrial thrombosis are known, including catheter-induced right atrial thrombosis (CRAT), which in different studies has an incidence of 2-29%, cases caused by valve implantation, which are more common in the right valves, and the cases are caused by the implantation of the leads of the intracardiac implantable devices (CIED). Mobile thromboses of the right atrium are a rare but life-threatening clinical scenario that has high diagnostic and therapeutic importance, and any delay in diagnosis can lead to death. Despite the many diagnostic methods, echocardiography is the most common method for diagnosing right atrial thrombosis [7-9]. In order to treat right atrial thrombosis, various treatment methods are known, but there is still no specific treatment guideline. Due to the fact that there is still no specific and single treatment for the treatment of right atrial thrombosis, in this study we are trying to investigate different treatment methods and compare them with each other and form a general result. In this study, we are trying to investigate and compare the treatment with fibrinolytics and surgical methods in terms of efficiency and side effects caused by them.

In 2020, Tran et al conducted a study to evaluate catheter complications in dialysis patients. In this retrospective study, 68 cases of CRAT in 63 patients were evaluated. After evaluations and data review, the results showed that the occurrence of right atrial thrombosis in patients can be one of the serious and main complications in patients. In addition, infection, fever and thrombocytopenia were other complications caused by catheter in patients. Finally, it was concluded that the use of fibrinolytic drugs in CRAT patients was associated with successful results, although in some cases it led to treatment failure that required rescue therapy [10].

In 2010, Janet et al conducted a study to evaluate the incidence and management of right atrial thrombosis in children. In this study, 122 patients were examined. After evaluations and data analysis, the results showed that removing the central venous catheter in patients without symptoms and with stable hemodynamics is a logical step if they have a catheter with or without anticoagulant treatment. Patients with symptoms were advised to receive anticoagulants. Regarding receiving fibrinolytic regimen or performing surgery, considering the risk of associated complications, it was recommended to make a decision based on the patient's condition [11].

In 2009, Burns et al conducted a study to evaluate and treat right atrial thrombosis. This study was a case report and a systematic review. After more evaluations and investigations, the results showed that there is a possibility of right atrial thrombosis and pulmonary embolism in patients when using the catheter. Finally, it was concluded that the use of thrombolytic drugs in patients can help in proper management of patients along with appropriate diagnostic methods [12].

Research Method

This study is in the form of a systematic review that was collected using the desired databases of articles. The databases used in this study

included PubMed, Google Scholar, Web of Science, and Embase.

Study population: The study population is all the articles published during the years 1980-2021 in different databases.

Place and time of study: Embase, PubMed, Web of Science and Google Scholar databases are in 1401.

Data collection method: In this study, keywords were first selected using MESH term, and after identifying the keywords, searches were performed based on the type of keyword.

Project implementation method: In this study, which is a systematic review, search strategies were determined using PICOTS criteria. Keywords, PICOTS criteria and search strategy are given in the appendix of the thesis. After determining the strategies, a search was conducted in four databases: PubMed, google scholar, embase and web of science. After selecting the articles, all the articles were collected in an EndNote library. After collecting, the desired articles were separated based on the

topic and type of study. After the initial separation and screening and identification of the original articles, the data were extracted from the desired articles. The selection of articles was based on the entry and exit criteria that are given in the following section. The articles were selected in such a way that at first the title and abstract of the articles were examined, and if the topic was relevant, full-text articles were taken and relevant information was extracted. The titles and abstracts of the articles were reviewed by two people, and finally the selected articles were re-reviewed by a third person. The investigated variables included age, gender, study year, authors, type of treatment, treatment result, clot size, type of fibrinolytic drugs, PTE and DX. Based on Figure 1, it is shown that 1541 articles were collected from several databases, and after removing duplicates, 964 articles remained, and finally, after removing irrelevant items, meta-analysis articles, letters to the editor, review articles and in cases whose language was other than English, the number of articles remained.

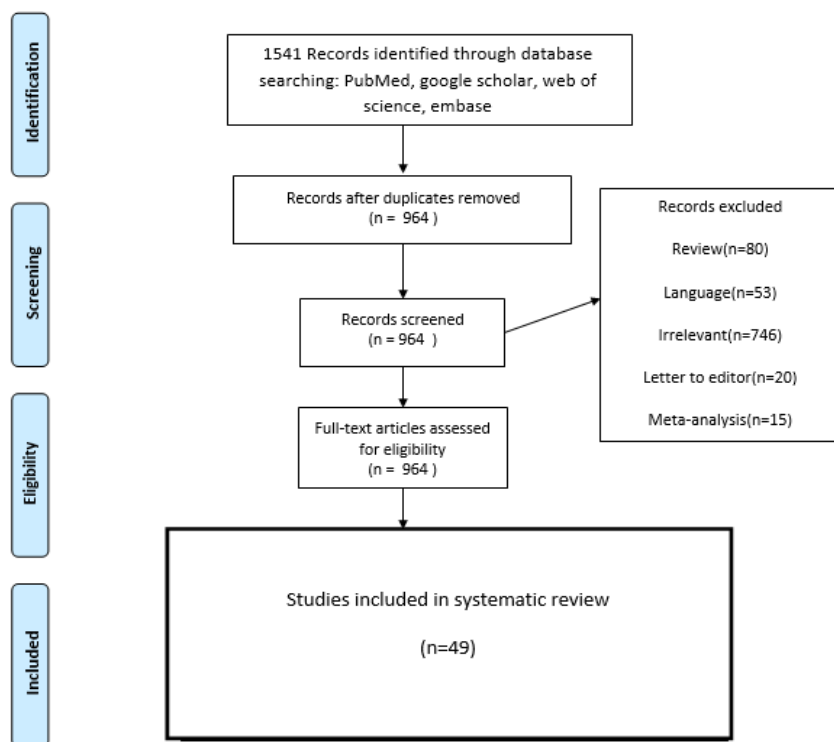


Figure 1. The process of selecting articles

Determining the sample size: According to the type of study, in this review, all the articles in the desired field that met the inclusion criteria were included in the study. Therefore, sampling methods were not used.

Inclusion criteria: Inclusion criteria include reviewed studies, right atrial thrombosis treatment methods, case report studies, and case series.

Exclusion criteria: Exclusion criteria include review studies, letters to the editor, animal studies, pediatric age group and treatment through percutaneous thrombectomy.

Ethical principles: In this study, which is a systematic review, the data obtained from the articles were recorded with complete mention of the sources and compliance with the publisher's rights. We also considered it necessary to use patient information only for research purposes.

Data analysis method: This study, which is a systematic review, was obtained based on articles obtained from relevant databases. In addition, in order to evaluate, treatment methods and their impact on the management of patients, their results were compared. The average age of the patients was reported in intervals. Also, treatments and treatment complications as well as clinical symptoms of patients were reported as percentages.

Limitations of the research: Among the limitations of the study, we can point to the lack of information in the articles related to patients, as well as full access to the articles (Full text).

Results

In the study conducted in 49 articles among 76 patients, the information of the patients was

collected, which includes the following information: Information related to age, sex, background disease, clinical picture of the disease, diagnosis method, treatment method, simultaneous embolism, thrombus size (quantitative or qualitative), hemodynamic status as stable or unstable, result as alive or dead and Year of publication and author of the article. 49 articles included 41 case reports and 8 case series. Also, the age range of patients varied from 19 to 95 years, and the number of women with right atrial thrombosis was more than men. The most common symptom and clinical presentation was shortness of breath. The most used diagnostic method was transthoracic echo. The most used treatment method was surgery. The information related to the age of the patients was collected in the age range of patients varied from 19 to 95 years.

Information related to gender segregation was collected in table (1) most of the people examined in the studies were women. (63% women and 37% men)

Table 1. Gender distribution

Frequency	Gender
28	Man
48	Woman

The information related to the underlying disease was collected in Table (2). In terms of the underlying disease, hypertension was the most frequent.

Table 2. Background disease

Bechet's disease	Renal disease	Diabetes	Blood pressure	COPD
4	11	8	15	8

The information related to the presence of simultaneous pulmonary embolism was collected in table number 5.51 of the subjects in the study had pulmonary embolism (67% had pulmonary embolism and 33% were without pulmonary embolism).

Table 3. Distribution of simultaneous pulmonary embolism

Frequency	Embolism
51	has
25	does not have

Information related to the distribution of therapeutic modalities (Table 3) was collected in Table 6. In terms of the type of surgical treatment, it was the most frequent. 35.5% of surgical patients, 32.8% of thrombolytic patients, 28.9% of anticoagulants and 0.02% of patients did not receive treatment (Table 4).

Table 4. Treatment distribution

Type of treatment			
Without Treatment	Antiqua Golan	Thrombolytic	Surgery
2	22	25	27
0.02%	28.9%	32.8%	35.5%

The information related to the distribution of thrombolytic type is collected in Table (5).

Table 5. Distribution of thrombolytic type

The thrombolytic type				
unknown	rTPA	TPA/alteplase	SK	TNK
3	4	7	10	1

The information related to clot size and treatment modality was collected in table (6). In total, in the studies conducted in 47 cases, RAT size was investigated, in 35 cases the size was reported quantitatively and in 12 cases it was reported qualitatively.

Table 6. Clot size – Treatment

The patient	Clot Size	Cure
43	28*3mm	Antiquagolan
46	1*1.3 cm	Antiquagolan
3	31*9 mm	Antiquagolan
19	30*12mm	rTPA
47	2.3*1.7cm	SK
7	3.85*1.15cm	surgery
5	19*22mm	Antiquagolan
10-5	2.5*2.1*1.3cm	Antiquagolan
29	56*13mm	surgery
10-2	3.1*2.5cm	surgery
34	3.1*2.8cm	Antiquagolan
28	9*1cm	surgery
2-2	36*25mm	surgery
30	3*3*1.5cm	surgery
10-1	3.5*3cm	surgery
24	4.24*2.21cm	TNK
40	3.7*3cm – 3.6*1.9cm	Antiquagolan
10-3	3.7*3cm	Antiquagolan
32	4.5*2.5cm	Antiquagolan
25	4.2*2.7cm	surgery
39	3.8*3.2*2.5cm	Antiquagolan
11	3.8*3.3cm	surgery
41	51*25mm	Alteplase
2-1	46*29mm	Antiquagolan
10-4	4.1*3.9cm	surgery
35	4*4cm	Antiquagolan
31	5.57*3.3*2.69cm	Antiquagolan
15	62*35mm	Antiquagolan
49	6*5.2cm	surgery
9-1	70*45mm	Antiquagolan

13	6*6cm	Antiquagolan
44	8*7cm	surgery
37	8*10cm	surgery
8	18cm long	surgery
18	1 meter long	surgery
1	Large and multiple	surgery
4	Large	TPA
12-1	Large	TPA
12-2	Large	surgery
14	Long	Antiquagolan
20	Large	TPA
21-1	Large	rTPA
23	Large	SK
36	Large	rTPA
27	Large	Antiquagolan
42	Large	Thrombolytic

Information related to patients with right atrial thrombosis and pulmonary embolism at the same time, as well as the type of modality received, were collected in table (7). 21 patients underwent surgery, 20 patients underwent thrombolytic therapy, 9 patients received anticoagulants, and 1 patient received no treatment. (41.17% surgery, 39.21% thrombolytic, 17.64% anticoagulant and 1.96% no treatment).

Table 7. Distribution of patients with simultaneous pulmonary embolism - type of treatment

The patient	Type of treatment
1	surgery
2-1	Anticoagulant
4	TPA
5	Anticoagulant
6-2	surgery
6-3	without treatment

6-4	surgery
6-5	surgery
6-6	surgery
6-7	Anticoagulant
6-8	surgery
6-9	surgery
6-10	Anticoagulant
6-13	surgery
7	surgery
8	surgery
10-3	Anticoagulant
10-4	surgery
11	surgery
12-1	TPA
12-2	surgery
13	Anticoagulant
16-3	SK
16-4	Anticoagulant
16-5	SK
16-6	SK
17	surgery
18	surgery
19	rTPA
21-1	rTPA
21-2	TPA
22-1	SK
22-2	SK
22-3	SK
23	SK
24	TNK
26	SK
27	Anticoagulant
28	surgery
29	surgery

30	surgery
31	Anticoagulant
33	surgery
36	rTPA
37	surgery
38	rTPA
41	Alteplase
42	Thrombolytic
44	surgery
45	Alteplase
47	SK

Gender distribution (relative percentage): 42.85% of deceased patients were male and 57.14% were female.

Gender distribution (absolute percentage): 8 out of 48 women died and 6 out of 28 men died.

Distribution of mortality based on treatment modality

- ✓ 5 cases underwent surgery (35.71%).
- ✓ 5 cases received anti-coagulant (35.71%).
- ✓ 2 cases received thrombolytics (14.28%).
- ✓ 2 cases did not receive treatment (14.28%).
- ✓ 2 out of 25 cases that received thrombolytics died (8%).
- ✓ 5 out of 27 cases that underwent surgery died (18.51%).
- ✓ 5 out of 22 cases who received anticoagulant died (22.72%).
- ✓ 2 of the 2 cases that did not receive treatment died (100%).
- ✓ 78.57% of patients with RAT who died had concurrent PTE.
- ✓ 40% of RAT patients who died had unstable hemodynamics.

Table 8. Mortality distribution

Number	The patient	gender	Thrombus size	Hemodynamics	PTE	cure	The cause of death
1	2-1	Woman	46*29mm	Stable	+	Anticoagulant	A 56-year-old dialysis woman was diagnosed with catheter and RAT infection and underwent anticoagulant treatment and was considered a candidate for elective surgery, but due to her unwellness and unstable hemodynamics, she underwent emergency surgery

							and died after surgery.
2	8	Man	18cm long	Stable	+	surgery	After the first surgery, she was operated again due to embolism, and she died after the second surgery.
3	10-2	Man	3.1*2.5cm	Stable	-	surgery	Post op CHF
4	10-3	Woman	3.7*3cm	Stable	+	Anticoagulant	PTE
5	10-4	Woman	4.1*3.9cm	Stable	+	surgery	After the surgery, she suffered an embolism and died.
6	6-3	Man	**	**	+	No treatment	-
7	6-8	Man	**	**	+	surgery	-
8	6-10	Woman	**	**	+	Anticoagulant	-
9	6-14	Man	**	**	-	No treatment	-
10	12-2	Man	Large	Stable	+	surgery	pulmonary infarction
11	16-2	Woman	-	Unstable	-	Anticoagulant	Contraindications for receiving surgery and thrombolytics
12	16-4	Woman	-	Unstable	+	Anticoagulant	Contraindications for receiving surgery and thrombolytics
13	21-1	Woman	Large	Unstable	+	rTPA	A 69-year-old woman with no history of heart disease died due to ICH after receiving rTPA despite the success of the treatment.

✓ Due to the fact that the thrombolytic treatment was successful in patient 48 and the patient died in the course of the treatment in the next few days, it is not

considered as mortality in the following data analysis.

Information related to the profile of patients with unstable hemodynamics was collected in table (8).

- ✓ Out of 76 cases, 62 patients' hemodynamic profile was mentioned, of which 16 patients had unstable hemodynamics (25.80%).
- ✓ Out of 16 patients with unstable hemodynamics, 4 died (25%).
- ✓ Out of 16 patients with unstable hemodynamics, 13 had simultaneous PTE (81.25%).
- ✓ Out of 16 patients with unstable hemodynamics, 11 patients received thrombolytic drugs and 2 died (18.18% of patients with unstable hemodynamics who received thrombolytics died).
- ✓ Out of 16 patients with unstable hemodynamics, 3 patients underwent surgery and had no mortality.
- ✓ Out of 16 patients with unstable hemodynamics, 2 patients received anticoagulants and both died.

Table 9. Unstable hemodynamics

Unstable hemodynamic profile				
Number	The patient	PTE	Death	Cure
1	1-16	-	survived	SK
2	2-16	-	died	Antiquagolan
3	4-16	+	died	Antiquagolan
4	5-16	+	survived	SK
5	18	+	survived	Surgery
6	1-21	+	died	rTPA
7	1-22	+	survived	SK
8	36	+	survived	rTPA
9	37	+	survived	Surgery
10	38	+	survived	Rtpa
11	41	+	survived	Alteplase
12	42	+	died	Thrombolytic
13	44	+	Survived	Surgery
14	45	+	Survived	Alteplase
15	47	+	survived	SK
16	*48	-	died	Alteplase

Due to the fact that the thrombolytic treatment was successful in patient 48 and the patient died in the course of the treatment in the next few days, it is not considered as mortality in the following data analysis. If we consider the reference table of patients with RAT chest pain, shortness of breath, syncope, palpitations and

cardiac arrest and consider the other patients without symptoms or with non-specific symptoms, the following table analyzes the patients without symptoms or with non-specific symptoms. Information about patients without symptoms or non-specific symptoms was collected in table (10). Out of 62 patients

(the information of 12 patients in article 6 was limited), 11 cases were without symptoms or specific symptoms (17.74%). 3 cases were operated (27.27 percent), one patient died, and 8 cases received anticoagulants (72.72 percent), and one patient died. Patients No. 3 and 43, who underwent balloon valvoplasty procedure due to severe mitral valve stenosis, had

asymptomatic right atrial thrombosis in the post-procedure phase, both of whom were successfully treated with anticoagulants. Patient No. 14, who was hospitalized with acute lower infarct and underwent two rounds of angioplasty, had asymptomatic right atrial thrombosis before discharge, which was successfully treated with anticoagulants.

Table 10. Asymptomatic patients

Number	the patient	embolism	mortality	Central venous catheter	cure	clinical manifestation
1	2-1	+	died	+	Anticoagulant	Blood culture +
2	2-2	-	survived	+	surgery	Transient bradycardia during dialysis
3	1-10	-	survived	+	surgery	Fever and chills
4	4-10	+	died	+	surgery	Fever
5	14	-	survived	-	Anticoagulant	Acute STEMI/Post PCI
6	15	-	survived	-	Anticoagulant	A case of cirrhosis and HCV who referred swelling of organs and ascites.
7	34	-	survived	-	Anticoagulant	A case of RCC presenting with weakness
8	35	-	survived	+	Anticoagulant	Fever
9	40	-	survived	+	Anticoagulant	Catheter infection
10	43	-	survived	-	Anticoagulant	Post PTMC
11	3	-	survived	-	Anticoagulant	Post PTMC

In the present study, after the evaluations and review of the articles based on the entry and exit criteria, 49 articles were finally selected. The reviewed articles were in the form of case reports (41 articles) and case series (8 articles), and each article examined a number of patients. From these articles, some patient information including age, gender, underlying disease, clot size, type of treatment, and the outcome of the patient's treatment were extracted. This information is shown in table number one [13]. Treatments used for right atrial thrombosis included surgery, the use of drugs such as

fibrinolytic drugs and anticoagulants. In some patients, the treatments were different based on the type of pathogenesis and their clinical conditions. Some patients required the use of antibiotics due to the presence of a specific underlying disease such as COPD [14-16].

In connection with the effectiveness and safety of the treatments, the results of the studies were also examined. Investigations showed that in general, in most studies, it has been shown that the use of fibrinolytic drugs in patients compared to surgery can be safer and have

better clinical outcomes for patients. In addition, along with fibrinolytic drugs, the use of anticoagulant drugs can have better outcomes for patients. Using the surgical method due to its invasiveness can have a series of complications for patients. Complications caused by surgery include the occurrence of infection, occurrence or exacerbation of heart failure, cardiac arrhythmia, bleeding and shock [17-19].

Discussion

The main pathogenesis of right atrial thrombosis is not fully understood. However, it has been shown that some cases are involved in its occurrence [20]. In general, it has been shown that the prevalence of right atrial thrombosis in patients is around 12.5%. However, in some patients, including patients using catheters, patients with infections, and those with coagulation disorders, the incidence of right atrial thrombosis is increasing [21-23]. Based on studies, it has been shown that the incidence of right atrial thrombosis in dialysis patients and those with malignancy due to the use of catheters is 5.4% and 8-13%, respectively. In addition to the factors mentioned above, which are involved in the pathogenesis of right atrial thrombosis.

Some other factors, such as endothelial cell disorders, juncture movement disorders, and some coagulation factor disorders can also play a role in the occurrence of the disease [24-26]. In terms of clinical symptoms, in some cases, patients are asymptomatic, however, in most cases, clinical symptoms are observed in patients, which include chest pain, shortness of breath, palpitations, and syncope [27-29]. There is a dual approach to the management of right atrial thrombosis and the choice of treatment approach is challenging. Several treatment options are available, including anticoagulation, embolectomy, and thrombolysis. The rate of success and survival of each approach varies depending on the clinical condition of the patient. The US Food and Drug Administration approved the Angio Vac aspiration system in 2009 [30-32]. Anticoagulation with heparin is generally considered the safest treatment, but its use has been associated with complications

such as thrombocytopenia. Rose et al reported a lower mortality rate in patients who received thrombolytic therapy compared with patients who underwent surgery or anticoagulation [33]. Theoretically, thrombolytic therapy has several advantages. Thrombolysis accelerates pulmonary reperfusion, lowers pulmonary artery blood pressure, improves right and left ventricular function, and improves cardiac hemodynamics [34].

Risks associated with thrombolysis include bleeding, hematoma formation, intracranial bleeding, the possibility of insufficient thrombolysis, and pulmonary embolism. Surgical embolectomy with examination of pulmonary arteries under complete cardiopulmonary bypass is the classic treatment [35-37].

There are many challenges and debates related to the treatment methods of patients with right atrial thrombosis [38]. However, until now, a suitable treatment method that has fewer side effects and is safer for patients has not been identified. In this study, we investigate the effect of different treatments of patients with right atrial thrombosis on their clinical outcomes as a systematic study. In a study conducted by Rose et al., it was shown that the mortality rate associated with anticoagulation treatment was 28.6%, treatment with a surgical approach was 23.8%, and thrombolysis treatment was 11.3%. In this retrospective study, 177 patients were examined [39].

Finally, it was shown that thrombolytic treatments were associated with increased survival for patients and were more appropriate compared to other treatments. In another study conducted by Barrios et al., it was shown that there was no significant difference in terms of mortality between two treatment methods using anticoagulants and reperfusion [40-42]. However, it was found that in the reperfusion method, the recurrence rate in patients was significantly higher. Also, there was no significant difference in the incidence of bleeding between the two groups. In another study conducted by Ruiez-bailen et al., it was shown that two patients with right atrial thrombosis who were treated with

thrombolytics did not respond to appropriate treatment. So, they underwent surgery. Regarding the use of tissue plasminogen activators, the results of Bajaj et al.'s study showed that it can improve the clinical conditions and survival of patients [43-45].

In the present study, 49 studies met the inclusion criteria. After the evaluations, the information about them is given in table number one, it was shown that different treatments were given in different studies [46-48]. This difference is due to the clinical conditions of the patients and the type of their disease. In addition, based on the underlying disease as well as clinical symptoms, different approaches and treatment strategies were adopted for each disease [49-51]. Results varied for the outcomes of each study. In general, based on table number one, it was shown that these results had a series of discrepancies [52-54]. In some studies, it was shown that the use of surgery had better outcomes for patients compared to anticoagulant and thrombolysis treatment. While some other studies showed that the use of anticoagulant and thrombolysis treatments had better outcomes for patients compared to surgery [55-57]. However, in general, the results of the studies showed that in most cases, the use of thrombolytic treatments has better results and fewer complications for patients compared to surgical treatment [57-61].

Conclusion

Finally, according to the data obtained from this study, it was shown that thrombolytics can be used for the treatment of patients with the same efficiency and less side effects compared to surgical treatment. The use of surgical method is recommended as the first treatment option in patients with unstable hemodynamics, suspected cardiac mass and cardiac anomaly (PFO).

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