ORIGINAL ARTICLE

Association between postoperative atrial fibrillation and the levels of hemoglobin or hematocrit: a systematic review and meta-analysis

İbrahim Öztürk, MD[1], Selen Öztürk, MD[2]

Medeniyet University Göztepe Education and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, (Turkey)
[2]Dr. Siyami Ersek Cardiovascular Surgery Education and Research Hospital, Department of Cardiovascular Surgery, Istanbul, (Turkey)

Correspondence: İbrahim Öztürk, MD, Medeniyet University Göztepe Education & Research Hospital, Department of Anesthesiology & Reanimation, Istanbul, (Turkey); Phone: +90 5333120185; E-mail: drozturk28@gmail.com

ABSTRACT

Objective: Postoperative atrial fibrillation is the most commonly observed arrythmia following cardiac surgery. Both atrial fibrillation and preoperative anemia hve been related to high rate of mortality and postoperative morbidity. In this systematic review and meta-analysis, we aimed to analyze whether levels of preoperative hemoglobin or hematocrit were useful biomarkers for development of postoperative atrial fibrillation after cardiac surgery or not.

Methodology: The literature screening was performed from PubMed database without any date limitation. All patients who underwent open cardiac surgery procedures were considered.

Outcome measures included the association between preoperative levels of hemoglobin/hematocrit and atrial fibrillation after cardiac surgery. The results of trials were evaluated with random or fixed effect model according to the heterogeniety. The statistical evaluation was performed by using Open Meta Analyst programme.

Results: A total of 9948 articles were found after database searching. 17 articles were included in meta-analysis consisting of 5934 patients who fulfilled inclusion criteria. The rate of postoperative atrial fibrillation was 35.6% (2114 cases out of 5934). Effect size was observed as heterogenous for studies including hematocrit (Q(df): 30.76, $p < 0.001$, I^2: 73.99%). However, it was not observed as heterogeneous for studies including hemoglobin (Q(df): 11.10, p: 0.26, I^2:18.96%). Analysis results of studies including hematocrit according to random effect model were SMD: 0.013, 95% CI -0.21-0.18 and p: 0.89 ($p > 0.05$). And analysis results of studies including hemoglobin according to fixed effect model were SMD: 0.172, 95% CI -0.23- -0.11 and $p < 0.001$.

Conclusion: The results of quantitative analysis showed that preoperative hemoglobin is associated with development of atrial fibrillation, but hematocrit is not. However, more studies may be required including both hemoglobin and hematocrit in the same trials to clearly establish this association.

Key words: Arrhythmias, Cardiac; Atrial Fibrillation; Hemoglobin; Hematocrit; Cardiac Surgery; Meta-Analysis

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INTRODUCTİON

Postoperative atrial fibrillation (POAF) is one of the most important event among postoperative complications and also it is the most commonly observed arrythmia following cardiac surgery. Vilareal et al[1] demonstrated that atrial fibrillation

had been an independent risk factor responsible for increasing in-hospital mortality, stroke and lenght of hospital stay after cardiac surgery.

The rate of POAF depends upon type of surgery (cardiac surgery or not) and also the type of applied cardiac surgical procedures. Incidence of POAF is approximately 3% after non-cardiac surgery, and changes between 9.8% - 74% after cardiac surgery.[2-4]

In recent studies, Miceli et al[5] reported that preoperative anemia had been related with increased rate of mortality and postoperative morbidity after cardiac surgery. The risk of death, postoperative renal dysfunction, postoperative stroke, atrial fibrillation and length of hospital stay > 7 days were greater than control group in anemic patients. Therefore, we hypothesized that preoperative levels of hemoglobin / hematocrit could be appropriate markers for prediction of atrial fibrillation. This study was aimed to analyze the association of preoperative hemoglobin or hematocrit for development of postoperative atrial fibrillation after cardiac surgery.

METHODOLOGY

Search strategy: We performed the database searching in accordance with the guideline of *Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).*[6] We used the electronic database search to determine whether the levels of preoperative hemoglobin or hematocrit could predict development of POAF after cardiac surgery or not. Two authors searched database until 16 February 2015. No limitation was set for publication date. PubMed was used as electronic database.

Key words or combinations of them (e.g. *cardiac surgery, heart surgery, valve surgery, coronary artery bypass grafting, postoperative atrial fibrillation, hemoglobin and hematocrit*) were used for searching. Searching was limited to English language only and the articles in other languages were excluded. The methods of studies were limited within the spheres of '*clinical trial, comparative study, multicenter study, observational study, randomized controlled trial, controlled clinical trial and evaluation studies'.*

Selection of studies: The studies, regardless of the sample size, included were retrospective or prospective clinical studies. Inclusion criteria were: (i) clinical study, (ii) open cardiac surgery with off-pump or extracorporeal circulation, (iii) article in English. Exclusion criteria were: (i) experimental studies or case series (ii) articles in other than English language, and (iii) non-cardiac surgery. The articles, associated with the issue of our review but not containing the knowledge about the levels of hemoglobin or hematocrit, were also excluded. Articles containing data with figures, not numerical values, were excluded.

Data extraction: Two reviewers independently extracted data from relevant studies. We extracted publication information (first author's name, publication year, patient population, type of surgery,sample size, type of study methods). Disagreement was resolved by consensus. The mean and standard deviations of both hemoglobin and hematocrit and sample size of groupswith POAF and without POAF were recorded as data.

We registrated to University of York Center of systematic reviews and dissemination. PROSPERO registration number is CRD42015023382.

Statistical analysis:

The meta-analysis programme, Open Meta Analysist, was used for statistical analysis. The standard mean differences (SMD) and 95% confidence interval (CI) was used for analysis. The heterogeneity was evaluated with the statistics of I^2. Heterogeneity was accepted as significant if $I^2 \geq 25\%$ and heterogeneity was evaluated with the analysis of moderators. Meta-analysis was applied by using fixed or random effect models. We performed random effect model in the presence of heterogeneity ($I^2 > 25\%$) and fixed effect model in absence of heterogeneity ($I^2 < 25\%$). Publication bias was evaluated with Begg test.

RESULTS

Flow diaphragm of database searching was shown in Figure 1.

Records identified through database searching were 9948 and records identified through database searching with filter were 4685. After duplicates were removed, 1019 records remained. Unrelated records (n=885) were excluded after screening. Full-text of 134 articles were assessed for eligibility and 117 of them were excluded because of absence of detailed data about hemoglobin and hematocrit in each group. 17 articles were included to quantitative synthesis.(7-23) Demographical features of studies were summarized in Table 1. The ratio of development of POAF was35.6% (2114cases of 5934).

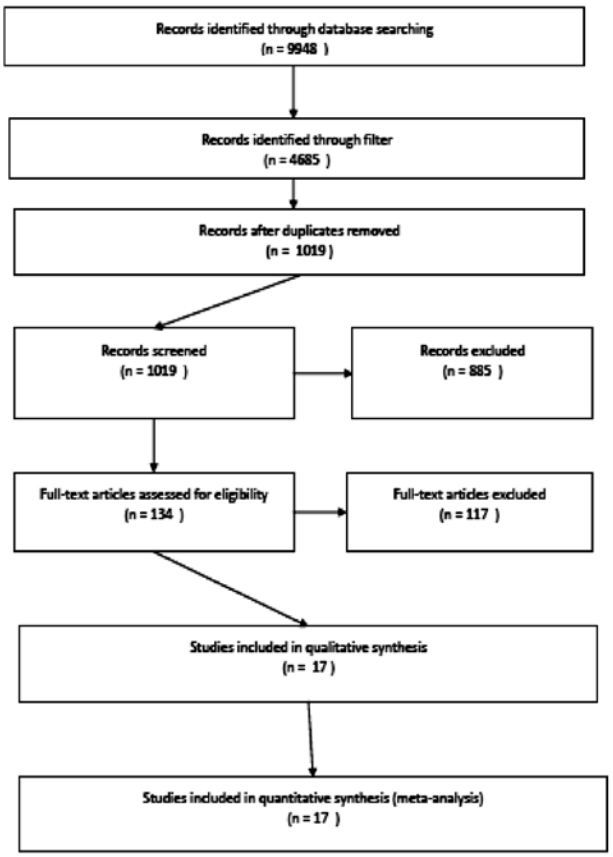

Figure 1: Flow diaphragm of search

Analysis results of studies including hematocrit according to random effect model were SMD: 0.013, 95% CI -0.21-0.18 and p: 0.89 (p>0.05). And analysis results of studies including hemoglobin according to fixed effect model were SMD: 0.172, 95% CI -0.23- -0.11 and p<0.001.

Effect size was observed as heterogeneous for studies including hematocrit (Q(df): 30.76, p<0.001, I2:73.99%). However, it was not observed as heterogeneous for studies including hemoglobin (Q(df): 11.10, p:0.26, I2:18.96%).Results were summarized in Figure 2 and 3.

The result of evaluation of publication bias was not significant for hematocrit including studies (tau ^{2}=0.06). However, there was publication bias for hemoglobin including studies (tau ^{2}=0.004).

The methods of studies (restrospective or prospective) and types of surgery (coronary artery bypass grafting surgery, valve surgery or combined CABG and valve surgery) were used as moderators for evaluation of the heterogeneity.Heterogeneity depended on the types of surgery (isolated CABGI^2 =74%, combined CABG and valve surgery I^2 =74%,) and the methods of trials (retrospective I^2 =91%, prospective I^2 =74%).

Table 1: Summary of studies included

Reference	Year	Study design	Surgery	POAF (n)	Non-POAF (n)
Abdelhadi[12]	2004	Prospective	CABG + valve	60	121
Güngör[15]	2011	Prospective	CABG	10	30
Hakala[16]	2002	Prospective	CABG	31	57
Lamm[19]	2006	Prospective	CABG + valve	99	154
Verdejo[21]	2011	Prospective	CABG + valve	32	112
Erdem[14]	2013	Retrospective	CABG	38	127
Almassi[7]	1997	Retrospective	CABG+ valve	1143	2712
Çetin[8]	2012	Prospective	CABG	62	210
Haghjoo[22]	2008	Prospective	CABG	46	256
Tanawuttiwat[23]	2014	Retrospective	Valve	52	71
Choi[13]	2009	Prospective	CABG	66	249
Kinoshita[17]	2011	Retrospective	CABG	121	431
Kinoshita[18]	2012	Retrospective	CABG	159	646
Pretorius[20]	2007	Prospective	CABG + valve	67	186
Şahin[10]	2014	Prospective	CABG	96	501
Şahin[9]	2010	Prospective	CABG	5	15
Güler[11]	2007	Prospective	CABG	27	56

atrial fibrillation and hemoglobin/hematocrit

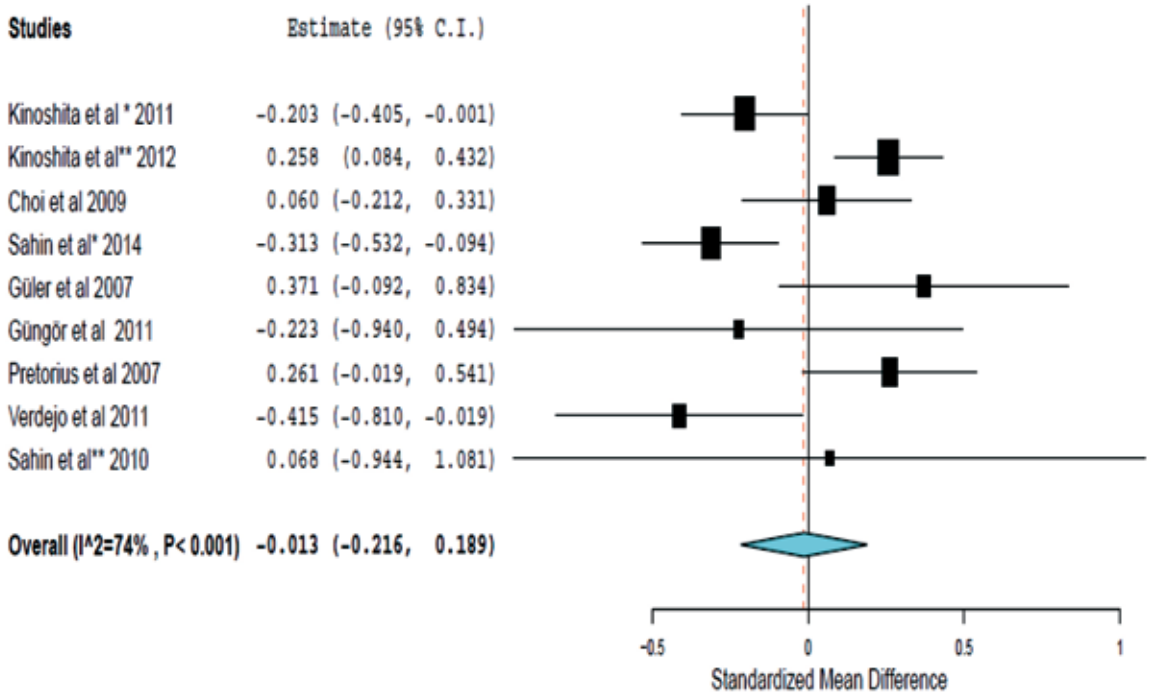

Figure 2: Analysis of studies including hematocrit

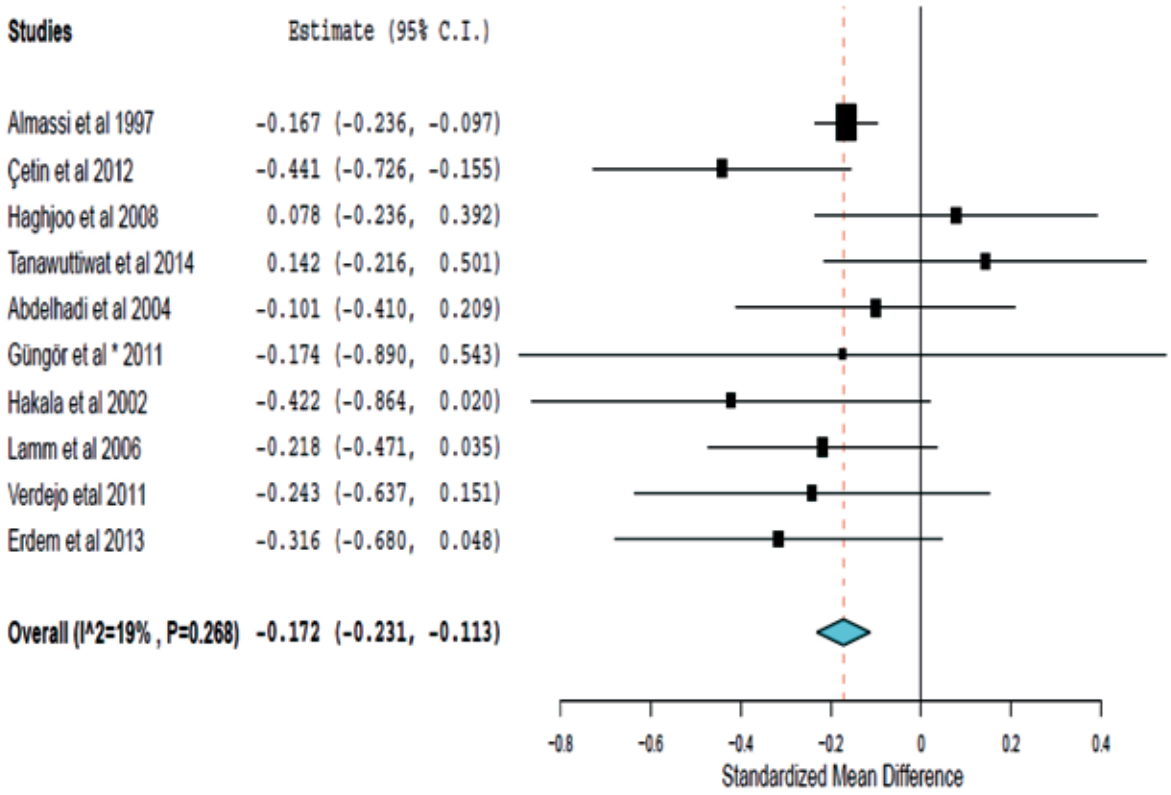

Figure 3: Analysis of studies including hemoglobin

DISCUSSION

World Health Organization[24] defined anemia as hemoglobin level lower than 12 g/dL in women and 13 g/dL in men.[24] However, varioussociodemographic and life style factors affect haemoglobin levels in pregnancy,[25] and also smoking can affect values of hemoglobin.[26] The mean hemoglobin levels for smokers are greater than non-smokers in both men and women.[26] In report of WHO prevalence of anemia is 30.2% for non-pregnant women and 12.7% for men.The prevalence of anemia in the surgical population has been reported as high as 24% in cardiac surgery.[5]

Preoperative anemia was associated with morbidity and mortality after cardiac surgery. In a recent study, preoperative anemia was demonstrated as an independent predictor of mortality and postoperative renal dysfunction and length of hospital stay > 7 daysin multivariable logistic regression.[5] On the other hand, Mirhosseini et al[27] showed anemia had not effect on the incidence of atrial fibrillation, early complications and mortality in patients undergoing off-pump CABG.[27] Chua et al[28] found anemia as a risk factor in univariate analysis but not in multivariate analysis for POAF. Hernández-Leiva et al[29] showed an association between POAF and hemoglobin with multivariate hemoglobin analysis (adjusted odds ratio:0.75 95% CI (0.28-2.01)).

For diagnosis and follow up anemia in clinical practice, both hemoglobin and hematocrit are usually used and also their levels can direct decision of blood transfusion.In this meta-analysis, we used two measures usually selected for diagnosis of anemia and also determination of blood transfusion decision in clinical practice. The accepted simple relationship between them is conventionally formulated as hematocrit (%)=hemoglobin (g/dL)x3.[29] However, conventional formula is not always accurate for all ages and for all levels of hemoglobin.[30] Flores-Torres et al[31] estimated the level of as hemoglobin=(Hematocrit/3.135)+0.257.

In our analysis, the main difference for prediction of POAF between preoperative hemoglobin and hematocrit, depends on the absence of fixed formula to convert them to each other. They must be seperately evaluated in those similar risk analysis. On the other hand, we think that the main reason of heterogeneous of studies including hematocrit smaller sample size of studies to evaluate POAF.

Determination of certain decision whether preoperative levels of hemoglobin or hematocrit predict POAF or not, is difficult because of two reasons. First, POAF is multifactorial complication of cardiovascular surgery. And second, limited numbers of trials that contain both hematocrit and hemoglobin in the same one.

Almassi et al[7] found POAF was associated not only with hemoglobin level and also with age, blood pressure, creatinin levels, cardiopulmonary bypass time and ischemic time in univariate analysis.In a current study, hematocrit anda ge is determined as predictors.[10] Çetin et al showed age and gender were also predictors of POAF.[8] Systemic diseases including diabetes mellitus[11,18] and chronic obstructive lung diseas[7] were found as risk factors for POAF in three studies.

The main predictor of POAF was age in most of the trials.[7,8,10-12,16-20,22] However age was not significantly related to POAF according to multivariate analysis in threetrials.[13-15,20]

Limitations:

The main limitation of our analysis was the limited data of studies. Except two studies[15,21] all of them included only hemoglobin or hematocrit. Therefore, it was difficult to analysis them on the same conditions (studies). Because of that reason, more trials about POAF including both preoperative hemoglobin and hematocrit levels, can certainly determine whether there is a difference between these measures or not.

CONCLUSION

Although there are limited studies, preoperative hemoglobin levels can predict POAF following cardiac surgery but not hematocrit. However, there is a need for more studies including both hemoglobin and hematocrit.

Conflict of interest: None declared by the authors.

Author Contribution: IO and SO shared concept, data acquisition, statistical analysis and manuscript preparation

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"Failure will never overtake me if my definition to succeed is strong enough".

Dr. A.P.J Abdul Kalam