

## Investigation of the Effect of Acute Normovolemic Hemodilution and Tranexamic Acid on the Amount of Bleeding During Off-Pump Coronary Artery Bypass Graft Surgery: a Systematic Review

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ARTICLE INFO	ABSTRACT
<p><b>Article type:</b> Review Article</p> <hr/> <p><b>Article history:</b> Received: 19- Feb-2015 Accepted: 05- July -2016</p> <hr/> <p><b>Keywords:</b> Acute normovolemic hemodilution Off-pump coronary artery Tranexamic acid</p>	<p><b>Introduction:</b> Bleeding and transfusion after open-heart operations are associated with morbidity and cost. To evaluate the effect of Acute Normovolemic Hemodilution (ANH) method and tranexamic acid on blood transfusion requirements and blood loss after Off-pump Coronary Artery Bypass surgery (OPCAB).</p> <p><b>Materials and Methods:</b> We searched The Cochrane Central Register of Controlled Trials, Medline, and Embase and retrieved articles published till December 2014. Afterwards, we manually searched the reference lists of published guidelines, reviews, and associated articles, as well as conference proceedings. We included all the articles with an available abstract in the English language. We manually searched the reference lists within the retrieved articles. Three reviewers independently reviewed and evaluated eligibility criteria and quality, as well as the extracted data.</p> <p><b>Results:</b> Bleeding and hemorrhagic complications and the consequent need for allogeneic transfusion are still major problems after OPCAB surgery that can be reduced with combination of ANH method and tranexamic acid.</p> <p><b>Conclusion:</b> Tranexamic acid and ANH appear to be effective in reducing postoperative bleeding and the need for allogeneic blood products.</p>

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### Introduction

Blood products are a scarce resource and expose patients to the risk of blood-borne diseases, graft-versus-host reactions, and acute hemolytic reaction, all of which increase the rate of patient morbidity and mortality (1).

Bleeding, hemorrhagic complications, and the consequent need for allogeneic transfusion are still major problems after cardiac surgery.

There are different strategies, including pharmacologic approaches and autologous blood transfusions, to reduce preoperative bleeding and the need for allogeneic transfusions.

The beneficial effects of tranexamic acid such as antifibrinolytic were shown in cardiac surgery in a large number of controlled trials (1-13). It is associated with less blood loss and requirement. It was shown to be effective in both on- and off-pump cardiac surgeries. Another approach is Acute Normovolemic

Hemodilution (ANH), which was introduced into surgical practice in the 1970s to reduce the requirement for blood transfusion.

The fundamental principle for ANH is the creation and tolerance of intraoperative anemia.

The preoperative dilution of circulating blood volume reduces the amount of red blood cells and plasma constituents lost during surgical bleeding.

It was suggested as an inexpensive and effective means of reducing allogeneic blood exposure in a report by the American Society of Anesthesiologists Task Force on blood component therapy. The efficacy of ANH, however, is uncertain. A meta-analysis performed by Bryson (14) and another one by Segal (15) regarding the role of ANH in reducing preoperative allogeneic transfusion showed that systemic reviews and statistical summary of published trials of ANH were inconclusive. As reduction of blood loss and preoperative transfusion is an important priority in cardiac surgery, we aimed to combine two different

approaches to determine whether their combination is more beneficial or not. The present study was designed to evaluate the effect of the combination of ANH and tranexamic acid on the reduction of blood loss and transfusion in patients undergoing Off-pump Coronary Artery Bypass graft surgery (OPCAB).

**Materials and Methods**

Articles were selected by searching journals of cardiothoracic surgery in MEDLINE. Our keywords and medical subject headings (OPCAB and ANH) were broad terms such as "off-pump coronary artery bypass " and " acute normovolemic hemodilution". The retrieved articles were hand-searched to identify additional related articles from their reference list. We included articles with available abstracts and in the English language that were published up to December 2014.

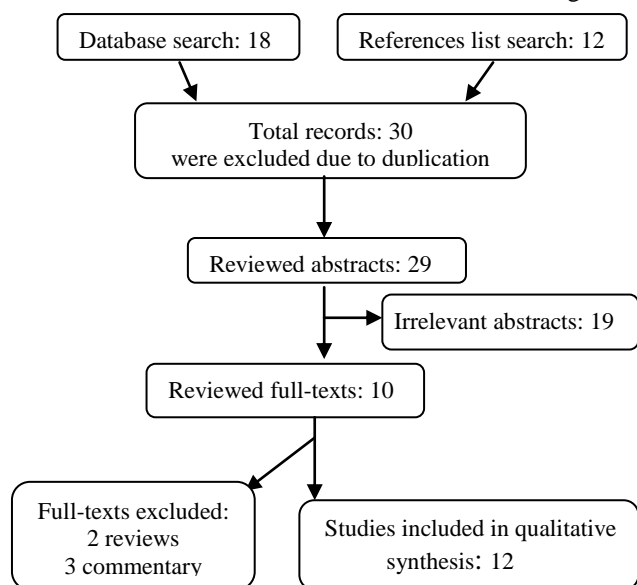
*Critical appraisal*

Firstly, abstracts were reviewed by two independent researchers. Twenty-nine abstracts were screened for relevancy twice, and 19 were excluded due to a lack of relevancy. The remaining 10 abstracts were fully assessed by our two reviewers.

With regards to article type, two case reports and three reviews were excluded from further evaluation. We used consort quality appraisal form to assess the quality of the selected articles. Two reviewers independently scored the quality criteria for each included study and a third reviewer resolved any discrepancies. We used a structural data extraction tool. However, due to heterogeneity in the main outcome measurements, meta-analysis was not performed.

**Results**

The flowchart of literature search is shown in Figure 1.



**Figure1: Flowchart of the literature search and study selection.**

The oldest study was published in 1998 and the most recent one in 2014. All the studies were conducted on a human model undergoing coronary artery bypass graft. Table 1 shows the general characteristics of the included studies.

**Table1: Summary of the nine studies included in the review**

Reference number	Year	Target population	Final result
17	2008	Patient undergoing off-pump coronary artery bypass (OPCAB)	Acute normovolemic hemodilution (ANH) significantly decreased the number of red blood cell units transfused
14	2005	Patient undergoing OPCAB	The beneficial effects of ANH in reducing the transfusion of allogenic blood in patients undergoing OPCAB
11	2007	Patient undergoing OPCAB	Tranexamic acid was more effective than auto transfusion in reducing postoperative blood loss and allogeneic transfusions after OPCAB
15	2009	Patient undergoing OPCAB	Intraoperative autologous blood donation in coronary artery bypass graft surgery decreased perioperative allogeneic blood requirements
10	2012	Patient undergoing OPCAB	Tranexamic acid reduced postoperative chest tube drainage and the requirement for allogeneic transfusion in OPCAB
9	2011	Patient undergoing OPCAB	Tranexamic acid reduced blood transfusion after OPCAB
8	2014	Patient undergoing OPCAB	The topical application of tranexamic acid in OPCAB patients led to a decreased postoperative blood loss
17	2004	Patient undergoing OPCAB	Preoperative ANH achieved further cardiac protection in patients undergoing on-pump myocardial revascularization.
19	2004	Patient undergoing OPCAB	The literature supported only modest benefits from preoperative ANH
20	2009	Patient undergoing OPCAB	Minimal ANH was safe and cost-effective and decreased perioperative allogeneic blood requirements

Almost all the studies confirmed the beneficial effects of tranexamic acid as an antifibrinolytic and ANH method in cardiac surgery, but the combination of the two methods was not studied (1-20). Although activation of fibrinolysis and platelet consumption are less in OPCAB than in cardiopulmonary bypass patients, net consumption of antithrombin, fibrinogen, and blood loss occur to a similar degree with the two types of surgery (7).

Therefore, excess bleeding requiring transfusion remains a major concern.

For this reason, in recent years, antifibrinolytic agents have gained widespread interest. Tranexamic acid was studied in different cardiac surgeries. Its beneficial effects to minimize bleeding and reduce exposure to blood products were determined in OPCAB surgeries (9). ANH is another technique that was suggested as an inexpensive and effective means for reducing allogeneic blood exposure.

## Discussion & Conclusion

The results of this systematic review and statistical summary of published trials of ANH are inconclusive (14-20). When considering all trials on ANH, it seems that ANH is effective in reducing both the likelihood of exposure to allogeneic blood and the volume of blood transfused. However, the presence of substantial and unexplained heterogeneity suggests that the benefit of ANH is inconsistent and cannot be definitively supported by this overview. Reasons for the inconclusive results include, the small sample size of the trials, pooling of trials from different surgical procedures, and variability in the amount of blood withdrawn preoperatively. The failure of trials using a transfusion protocol to demonstrate a statistically significant benefit suggests that biased study design may be responsible for the reduction in blood exposure attributed to ANH.

There has been an increasing interest in tranexamic acid in recent years. The beneficial effects of antifibrinolytic agents during cardiac surgery to

minimize bleeding and lower exposure to blood products were determined.

A meta-analysis by Brown (1) also indicated that all antifibrinolytic agents were effective in reducing blood loss and transfusion. Casati (5) and Wei (6) investigated the effect of tranexamic acid in patients undergoing OPCAB surgery. Casati (5) showed that tranexamic acid was effective in reducing postoperative bleeding and the need for allogeneic blood products. Wei (6) also demonstrated that cumulative blood loss was significantly reduced in the tranexamic acid group as compared with the controls postoperatively, but the number of patients receiving blood transfusion in each group was similar.

During treatment with an antifibrinolytic agent like tranexamic acid, there is a theoretic risk of increased thrombotic events affecting cardiovascular, cerebrovascular, and renal outcomes.

Casati (5) and Wei (6) did not observe any major adverse events and thrombotic complications. In the present study, the authors did not notice any cerebrovascular, cardiovascular, or renal dysfunction.

Based on the results of the previously mentioned studies, as well as many other studies (1-13), it appears that tranexamic acid is a safe adjunct in OPCAB surgery, and perhaps because of the recent findings about renal dysfunction and mortality associated with aprotinin, more attention should be given to tranexamic acid in future. It seems that larger trials with carefully defined indications for the transfusion of allogeneic blood are required to establish the efficacy of this technique. The fundamental principle of ANH is the creation and tolerance of intraoperative anemia. Morbidity and mortality were shown to increase as hemoglobin level decreases below 100 g/L, with the risk further increased in patients with preexisting cardiovascular disease (7).

Although no increase in adverse events was noted in patients receiving ANH, the poor reporting of these outcomes suggested that the results of this overview cannot be used to establish the safety of this technique.

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