ΠΑΝΕΠΙΣΤΗΜΙΟ ΘΕΣΣΑΛΙΑΣ

ΤΜΗΜΑ ΙΑΤΡΙΚΗΣ

ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
ΜΕΘΟΔΟΛΟΓΙΑ ΒΙΟΪΑΤΡΙΚΗΣ ΕΡΕΥΝΑΣ, ΒΙΟΣΤΑΤΙΣΤΙΚΗ ΚΑΙ ΚΛΙΝΙΚΗ ΒΙΟΠΛΗΡΟΦΟΡΙΚΗ

Μεταπτυχιακή διπλωματική εργασία

Αξιολόγηση τυχαιοποιημένων κλινικών μελετών για τη χρήση του τρανεξαμικού οξέος στις ολικές αρθροπλαστικές ισχίου, από το 2015 έως και το 2019, με τη χρήση του CONSORT statement

Assessment of reporting quality of RCTs reported from 2015 to 2019 for efficacy and safety of Tranexamic acid (TXA) in patients undergoing total hip arthroplasty (THA) based on CONSORT statement

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Λάρισα 2019

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ABSTRACT

Background: Randomized controlled trials (RCT) provide the strongest evidence to justify interventions in patients. However, clinical trials with inadequate methods or interpretation of methods and results are associated with bias and exaggerated treatment effects. Therefore, there is need not only for correctly implemented studies, but also for well reported studies. In order to improve the quality of reporting of clinical trials, the Consolidated Standards of Reporting Trials (CONSORT) statement has been developed.

Objectives: The main objective of this study was to assess the reporting quality of RCTs reported from 2015 to 2019 for efficacy and safety of Tranexamic acid (TXA) in patients undergoing total hip arthroplasty based on the consolidated standards of reporting trials (CONSORT) statement.

Methods: A PubMed search for RCTs published from 2015 to 2019 was performed. We selected articles that evaluated the safety and efficacy of Tranexamic Acid (TXA) in reducing blood loss after total hip arthroplasty. Eligible articles were assessed according to checklist of CONSORT statement 2010 and the data were processed with descriptive and analytical statistics.

Results: A total of 18 RCTs were included. About 25 CONSORT items (67.5 %) were mentioned in more than 50% of the studies when the average CONSORT score of referred items was 23 out of 37 items (62.1%). Reporting above 75% of the items was defined as adequate compliance to the CONSORT statement. From the linear regression analysis, a statistically significant model was concluded, which explains the prediction of CONSORT score according to the journal Impact factor.

Conclusions: RCTs for efficacy and safety of Tranexamic acid (TXA) in patients undergoing total hip arthroplasty were found to be moderately reported. Compliance to CONSORT statement is undoubtedly a way to insure a good reporting quality that will drive to generally accepted and applicable results in clinical practice.

Keywords: Total hip arthroplasty, tranexamic acid, CONSORT statement, quality of reporting, randomized clinical trials.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι τυχαιοποιημένες κλινικές μελέτες παρέχουν τα πιο αξιόπιστα στοιχεία, τα οποία χρησιμοποιούνται σε παρεμβάσεις σε ασθενείς. Παρόλα αυτά, κλινικές μελέτες με ανεπαρκείς μεθόδους ή ανεπαρκή ερμηνεία μεθόδων και αποτελεσμάτων, σχετίζονται με σφάλματα και ανεπιθύμητα θεραπευτικά αποτελέσματα. Επομένως, προκύπτει ανάγκη, όχι μόνο για ορθά εφαρμοσμένες μελέτες αλλά και για ορθά γραμμένες μελέτες. Προκειμένου να βελτιωθεί η συγγραφική ποιότητα των κλινικών μελετών, αναπτύχθηκε το CONSORT statement.

Στόχοι: Ο βασικός στόχος αυτής της εργασίας είναι να αξιολογήσει την συγγραφική ποιότητα τυχαιοποιημένων κλινικών μελετών που αφορούν στη χρήση του τρανεξαμικού οξέος στις ολικές αρθροπλαστικές ισχίου, από το 2015 έως και το 2019, με τη χρήση του CONSORT statement.

Μέθοδοι: Πραγματοποιήθηκε αναζήτηση στη βάση δεδομένων PubMed για δημοσιευμένες τυχαιοποιημένες κλινικές μελέτες από το 2015 έως το 2019.Επιλέχθηκαν μελέτες που αξιολογούσαν την ασφάλεια και την αποτελεσματικότητα του Τρανεξαμικού οξέος στη μείωση της απώλειας αίματος μετά από ολικές αρθροπλαστικές ισχίου .Κατάλληλες μελέτες αξιολογήθηκαν με βάση το ερωτηματολόγιο CONSORT 2010,και τα αποτελέσματα αναλύθηκαν με μεθόδους περιγραφικής και αναλυτικής στατιστικής.

Αποτελέσματα: Συνολικά αναλύθηκαν 18 μελέτες.25 από τα αντικείμενα του CONSORT (67.5 %) είχαν αναφερθεί σε περισσότερες από τις μισές (50%) μελέτες ενώ ο μέσος όρος του CONSORT score των αναφερθέντων αντικειμένων ήταν 23 στο σύνολο των 37 (62.1%).Ως καλή συγγραφική ποιότητα θεωρήθηκε το CONSORT score μεγαλύτερο του 75%.Από την ανάλυση γραμμικής παλινδρόμησης βρέθηκε ένα στατιστικά σημαντικό μοντέλο ,με το οποίο μπορεί να προβλεφθεί το CONSORT score λαμβάνοντας υπόψη το Impact Factor του εκάστοτε περιοδικού.

Συμπεράσματα: Οι τυχαιοποιημένες κλινικές μελέτες που αφορούν στη χρήση του τρανεξαμικού οξέος στις ολικές αρθροπλαστικές ισχίου, από το 2015 έως και το 2019,βρέθηκε να έχουν μέτρια συγγραφική ποιότητα, δείχνοντας ότι σε πολλές μελέτες ακόμη υπάρχει έλλειψη καλής συγγραφικής ποιότητας. Η συμμόρφωση με τους κανόνες του CONSORT είναι αναμφίβολα ένας τρόπος βελτίωσης της συγγραφικής ποιότητας η οποία θα οδηγήσει σε ορθά και εφαρμόσιμα συμπεράσματα στην κλινική πράξη.

Λέξεις κλειδιά: Ολική αρθροπλαστική ισχίου, τρανεξαμικό οξύ, CONSORT statement, συγγραφική ποιότητα, τυχαιοποιημένες κλινικές μελέτες.

INTRODUCTION

A randomized controlled trial (RCT) is a type of scientific experiment that aims to reduce sources of bias when testing the effectiveness of new treatments or evaluating the efficacy of new therapeutic or preventive interventions. This is accomplished by randomly allocating subjects to two or more groups, treating them differently, and then comparing them with respect to a measured response [1, 2].

RCTs are considered as a gold standard in clinical medicine and public health. Clinicians tend to make conclusions, change their decision-making process and treatment guidelines in everyday clinical practice, according to evidence-based information from RCTs that has to be properly designed, but also conducted and reported in a standard way [1, 2].

In order to insure the generalizability, external validity, and applicability of the trial findings, there is a need for transparent information about methodology and findings of clinical trials. It becomes necessary to assess not only the methodological quality of all trials but also the quality of reporting. A poor reporting may often lead to biased conclusions and furthermore make it difficult for scientists to implement the results in everyday clinical practice [3].

The alleviation to the problems arising from inadequate reporting of randomized controlled trials came from the CONSORT Group (Consolidated Standards of Reporting Trials). The main product of CONSORT is the CONSORT statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation [3].

The CONSORT statement is endorsed by prominent general medical journals, many specialty medical journals, and leading editorial organizations. CONSORT is part of a broader effort, to improve the reporting of different types of health research, and indeed, to improve the quality of research used in decision-making in healthcare [3].

In the bibliography, there are review articles concerning quality reporting assessment of RCTs in several medical domains. However, there is a lack in quality reporting assessment when focusing on the new blood saving strategy with tranexamic acid (TXA) in one the most common orthopedic procedures, the total hip replacement [4-6].

Total hip arthroplasty is associated with significant blood loss, anemia and transfusion, delaying recovery and increased mortality. Blood reducing strategies,

such as antifibrinolytic agents have been applied in order to reduce blood transfusions and their consequences; infections, immunologic reactions, and other [8,9].

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine, which competitively inhibits plasminogen, leading to reduced fibrinolysis of existing thrombus. The efficacy and safety of TXA in reducing blood loss have been demonstrated in many types of surgery. However the best treatment regimen has yet to be established, and this is the reason why there is already a lot of RCTs and need for further research to come. An assessment of the quality of these trials is essential to ensure the applicability of their findings in clinical practice and can be accomplished via a thorough reporting of their methodology, conduct, data analysis and results [10-27].

The main objective of this study was to assess the reporting quality of RCTs that explore the efficacy and safety of Tranexamic acid (TXA) in patients undergoing total hip arthroplasty, based on CONSORT checklist 2010.

METHODS

Search strategies and data sources

PubMed was searched for RCTs concerning TXA in total hip arthroplasty, from 2015-2019.The following terms in advanced search were used: ((TXA) OR Tranexamic acid) OR fibrinolytic factors vs placebo) AND total hip arthroplasty) NOT knee arthroplasty as well as ((TXA) OR Tranexamic acid) OR fibrinolytic factors VS placebo) AND total hip arthroplasty) AND secondary hip arthroplasty) AND primary hip arthroplasty NOT knee arthroplasty. The filters used were: “Clinical trial”, “5 years” and the language was “English”.

Studies selection

The first screening was in titles and abstracts. Eligible studies were these which had at least two treatment groups and patients were randomized. The objective of the studies that we finally assessed was: Investigation of safety and efficacy of TXA in reducing blood loss in patients undergoing total hip arthroplasty (without considering the way of administration). Except for Randomized Clinical Trials, all the other studies such as Retrospective studies, Reviews, Letters to the editor and abstracts without full text accessible were excluded. We also excluded pooled analyses, non-English trials and reports of trial protocols. When several reports referred to the same trial, only the major trial report was included.

Data extraction and reporting assessment tool

The assessment for the quality of reporting has been done by one person using the revised CONSORT checklist, which includes a 25-item (37-item/sub-item) questionnaire. As checklist items focus on reporting how the trial was designed, analyzed, and interpreted, we investigated them and accepted as positive only the reported ones. Positive answers were the clearly reported items and especially for three items [specific dates (14a), outcome measure (6a) and study design -allocation ratio (3a)], we were not strict, as we considered them as positive, even if there were not fully reported as in CONSORT checklist. Also, when an article was using just a reference for describing the methods and results, then the relevant items were considered as reported. On the other hand, items not reported at all were considered as negative.

Evaluation and article scoring

We evaluated all selected articles step by step following CONSORT checklist:

- ”Title and abstract”

(1a, 1b): Identification of the randomized trial in the title and a structured summary of the whole trial

- "Introduction"

(2a, 2b): Scientific background and explanation of rationale and specific objectives or hypotheses

- "Methods"

(3a): Reporting of description of the trial design including allocation ratio

(3b): Important changes to methods after trial commencement with reasons

(4a): Eligibility criteria for the participants

(4b): Settings and locations where the data were collected

(5): Interventions for each group with sufficient details to allow replication, including how and when they were actually administered

(6a): Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed

(6b): Changes to trial outcomes after the trial commenced, with reasons

(7a): How sample size was determined

(7b): When applicable, explanation of any interim analyses and stopping guidelines

(8a): Method used to generate the random allocation sequence

(8b): Type of randomization; details of any restriction

(9): The mechanism used to implement the random allocation sequence, describing any steps taken to conceal the sequence until interventions were assigned

(10): Who generated the random allocation sequence who enrolled participants, and who assigned participants to interventions

(11a): If done, who was blinded after assignment to interventions and how

(11b): If relevant, description of the similarity of interventions

(12a): Statistical methods used to compare groups for primary and secondary outcomes

(12b): Methods for additional analyses, such as subgroup analyses and adjusted analyses

- "Results"

(13a): Numbers of participants who were randomly assigned in each group, received intended treatment, and were analyzed for the primary outcome

(13b): Losses and exclusions after randomization, together with reasons

(14a): Dates defining the periods of recruitment and follow-up

(14b): Why the trial ended or was stopped

(15): A table showing baseline demographic and clinical characteristics for each group

(16): Number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

(17a): For each primary and secondary outcome, results for each group, and the estimated effect size and its precision

(17b): For binary outcomes, presentation of both absolute and relative effect sizes is recommended

(18): Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

(19): All important harms or unintended effects in each group

- "Discussion"

(20): Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

(21): Generalizability of the trial findings

(22): Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

- "Other information"

(23): Registration number and name of trial registry

(24): Where the full trial protocol can be accessed, if available

(25): Sources of funding and other support, role of funders

Compliance of each RCT with the 37-item CONSORT checklist was scored by one person. For each item, RCTs scored either: 1-reported; 0-not reported. RCTs scored "1" for an item if all or some information have been reported, and "0" if the required information was not reported.

Then a sum of all scores was calculated and statistical analysis was conducted. Firstly, we made comparisons between items of CONSORT checklist and secondly we took into account some other factors that affected the reporting quality and the final score; Journals Impact Factor and publication year.

Statistical analysis and subgroup analysis

A total score of reporting CONSORT items was calculated by adding up the scores of the 37 items and then using descriptive statistics we calculated mean and percentage for each item. Compliance above 75% was defined as adequate.

A second analysis was a subgroup analysis comparing the CONSORT scores of all studies according to the impact factor of the journal where studies were published. For the comparison of continuous data between two subgroups, we used the t-test for normal distributed data. P-values were two-tailed and P-values <0.05 were considered statistically significant. The data were normally distributed.

Additionally, Univariate analysis was conducted to investigate the association of two factors with CONSORT compliance in our sample. Factors investigated for inclusion in a Multivariate Logistic Regression analysis were: journal impact factor and year of publication.

A Linear regression analysis was conducted to investigate if there is linear relationship between CONSORT compliance and Impact Factor. Pearson Correlation Coefficient (Pearson's r) was used for this purpose.

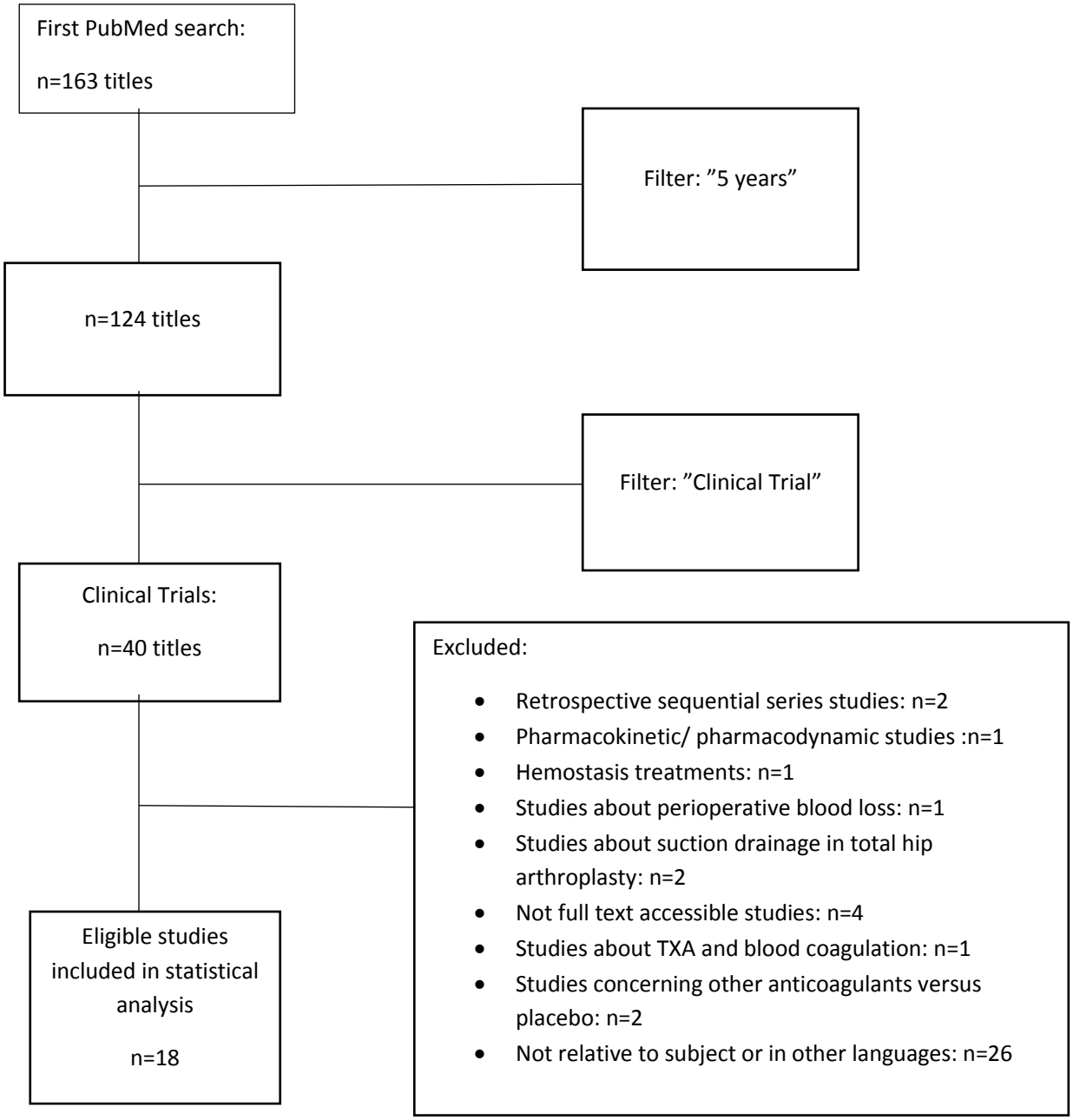
All data were analyzed using Microsoft Excel Software (Version 15.23, 2016, Microsoft).All statistical analyses were performed using Statistical Package for Social Sciences (SPSS v.25.0).

RESULTS

Eligible studies

First search retrieved 163 titles. After adjusting the filter “5 years”, the titles retrieved were 124, and finally, only 40 of them were clinical trials, after adjusting the filter “clinical trial”. From these articles only 18 studies were eligible and were included in statistical analysis. In detail, the retrieval and screening process is shown below in the flow diagram [Figure 1].

Figure 1: Flow diagram of citations through the retrieval and screening process.



Main results

The frequency of reported CONSORT items was between 0 % - 100 %.

From CONSORT checklist most reported items were: 1, 2a 4a, 5, 12a, 15 and 19 and less reported items were: 3b, 4b, 6b, 7b, 10, 12b, 14b, 17, 18, 21, 24.

Particularly 5 items (13.5 %) were mentioned in 100% of the studies: 1b, 2a in the abstract and introduction, 4a in methods, 12a in randomization and 15 in results.

A number of 8 items (21.6 %) were reported by 90% or more of the studies: 1a, 1b in the title and abstract, 2a in the introduction, 4a, 5 in methods, 12a in randomization, 15, 19 in the results.

Also, about 25 items (67.5 %) were mentioned in more than 50% of the studies. [Table 1]

On the other hand, there are 12 items in CONSORT statement that were mentioned by a proportion less than 50% (32.4%) such as: 4b about settings and locations where the data were collected, item 10 concerning implementation, 12b about additional and subgroup analysis, item 17 concerning the outcomes, 18 concerning analysis, 21 about generalizability of outcomes, 24 about accessible protocol.

In the end, the items that were not mentioned at all were: 3b about important changes to methods, 6b about changes to trial outcomes, 7b about interim analyses and stopping guidelines, 14b about the end of the trial. These items, in most studies were not referred because they were not implemented, but we assessed them as negative because they were not reported.

The CONSORT score was calculated for each study as a summary of referred items in a total of 37 items of CONSORT checklist. The CONSORT score's mean was calculated as the average of 18 CONSORT scores and was 23/37 (62.1%), SD=5.87 with minimum score 11 and maximum 32.

Among the retrieved studies only 4 studies presented a CONSORT score above 75%.

The impact factors in selected studies were between 0.1 (minimum) and 5.1 (maximum) with mean impact factor 2.9.

A subgroup analysis was conducted between studies with IF<3 and those with IF>3. We chose the mean impact factor as the cut-off point. A comparison of CONSORT scores' mean between these subgroups was conducted with Independent sample t-test, for normal distributed data (Shapiro Wilk test: p value=0.3>0.05) [Table 2].

There was no statistical difference in CONSORT score between studies published in journals with impact factor >3 and studies published in journals with impact factor <3. (p value = 0.183 >0.005)

In the Univariate analysis, we found no significant relation between CONSORT score and the year of publication (p =0.78>0.05). On the contrary we found significant association between CONSORT score and IF (p=0.03<0.05).

We conducted a Linear Regression Analysis to investigate for linear relationship between CONSORT compliance and IF. A statistically significant correlation was established [Pearson Correlation Coefficient (Pearson's r) = 0.517, p value<0.05)] .In the linear regression model the coefficient of determination (R^2) was found to be R^2= 0.267, which means that 26.7% of the variance in the dependent variable (CONSORT score) is predictable from the independent variable (IF). The regression model was**:** (CONSORT score) =17.134 +2.015 *(IF) with P value $_{(constant)}$ <0.05 and P value $_{(IF)}$ = 0.028<0.05.

With the above model the CONSORT score can be predicted according to the journal Impact factor.

There were also other factors that we could take into account in our model such as sample size or consort endorsement reported in the studies, but we concentrated only in the two factors above. The investigation of other predictors could be the subject of other studies.

Table 1 shows the overall frequency of reporting of the 37 items/sub-items of the CONSORT statement.

Table 1. Reporting of CONSORT items

CONSORT Section/topic	Item No	All Trials N=18	Frequency (%)
Title and abstract	**1a**	17	94.4
	1b	18	100
Introduction			
Background and objectives	**2a**	18	100
	2b	15	83.3
Methods			
Trial design	**3a**	14	77.8
	3b	0	000
Participants	**4a**	18	100
	4b	6	33.3
Interventions	**5**	17	94.4
Outcomes	**6a**	16	88.9
	6b	0	0.00
Sample size	**7a**	13	72.2
	7b	0	0.00
Randomization			
Sequence generation	**8a**	16	88.9
	8b	10	55.6
Allocation concealment	**9**	10	55.6
Implementation	**10**	6	33.3
Blinding	**11a**	15	83.3
	11b	12	66.7
Statistical methods	**12a**	18	100
	12b	5	27.8
Results			
Participants	**13a**	16	88.9
	13b	12	66.7
Recruitment	**14a**	11	61.1
	14b	0	0.00
Baseline data	**15**	18	100
Numbers analyzed	**16**	15	83.3
Outcomes	**17a**	6	33.3
	17b	2	11.1
Ancillary analysis	**18**	5	27.8
Harms	**19**	17	94.4
Discussion			
Limitations	**20**	16	88.9
Generalisability	**21**	5	27.8
Interpretation	**22**	16	88.9
Other information			
Registration No	**23**	16	88.9
Protocol	**24**	4	22.2
Funding	**25**	13	72.2

Table 2. Factors included in regression models.

Study	Year	Impact Factor	CONSORT score
study1	2018	3.2	22
study2	2018	3.2	24
study3	2019	4.7	25
study4	2017	4.3	22
study5	2018	2.7	23
study6	2016	4.8	21
study7	2018	1.9	21
study8	2017	1.3	16
study9	2017	3.5	24
study10	2019	0.8	13
study11	2018	2.3	20
study12	2019	4.3	30
study13	2018	1.2	30
study14	2017	1.8	32
study15	2017	4.3	23
study16	2017	0.1	11
study17	2017	5.1	32
study18	2016	3.4	26

DISCUSSION

The present study investigated the reporting quality of RCTs concerning the efficacy and safety of TXA in blood loss in patients undergoing total hip arthroplasty based on the CONSORT statement. Although reporting quality does not affect the actual quality, the design and methods of the study, it remains a factor that assesses the total study quality.

The average CONSORT score of reported items was 23 (62.1%) with SD=5.87, which means that more than 50% of CONSORT items were reported in a total of 18 evaluated studies, but less than 75%.We concluded that the quality of reporting was moderate to good but still unsatisfactory [4-7]. It is very important to have a high reporting CONSORT score in general, which means an accepted reporting quality, because that affects medical and scientific community who extract useful information for patients and they can be influenced in their decision making process in every day clinical practice.

The present study has some limitations: firstly, only articles published in English were considered, which may lead to language bias. In addition, the research has been restricted in PubMed, the most commonly used database in medicine. Furthermore, the data extraction and article evaluation were made only by one person without comparison and verification of the results from someone else. Additionally, only full text articles were analyzed, rejecting abstracts and in this way some information was lost. Some items were reported as positive, even if there were not fully reported as in CONSORT checklist. For example, we were not strict with specific dates (14a), with outcome measure (6a) and with the study design and allocation ratio (3a). Also, when an article was using just a reference for describing the methods and results, then the relevant items were considered as reported. This maybe was the reason for higher reporting quality than expected. Finally, the sample size of 18 studies was too small. That was a problem not only in the analysis but also in the generalizability of the results.

Particularly, regarding the study results, CONSORT score's mean was calculated 23 (11- 32). From CONSORT checklist most reported items were: 1, 2a 4a, 5, 12a, 15 and 19 and less reported items were: 3b, 4b, 6b, 7b, 10, 12b, 14b, 17, 18, 21, 24. In detail, authors are more precise when referring to basic items of the article study: title, abstract, rationale, objectives, eligibility criteria of patients, statistical methods, baseline demographic characteristics and harms. On the other hand writers do not emphasize in items such as settings and locations where the data were collected,

random allocation sequence, enrollment of participants, results for each group, and the estimated effect size and its precision (such as 95% confidence interval).

Taking into account and comparing the other characteristics of the 18 selected studies, such as Journals Impact Factors and publication year, we tried to find if there is relation between them and the CONSORT score and if the CONSORT compliance can be predicted by these factors.

The analysis revealed that there is statistically significant relation between CONSORT score and Impact Factor described with a linear regression model. However, other possible coefficients or predicting factors, were not calculated in this model.

In addition to our study, supplementary analysis and investigation can be conducted. Other factors such as, sample size, sources of funding or number of authors that may possibly affect reporting quality can be further investigated.

The compliance to CONSORT guidelines from more and more authors in scientific journals will undoubtedly improve the reporting quality, and will drive to not only generally accepted but also widely applicable results that will affect clinical practice and interventions to patients.

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