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Διπλωματική εργασία

Αξιολόγηση της ποιότητας αναφοράς των Τυχαιοποιημένων Κλινικών Δοκιμών για τα αντιπηκτικά φάρμακα σε καρκινοπαθείς ασθενείς με τη χρήση της δήλωσης CONSORT

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Assess the reporting quality of RCTs for anticoagulant drugs in cancer patients using the CONSORT statement

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Στην οικογένειά μου

Contents

1. Abbreviations

CONSORT - Consolidated Standards of Reporting Trials
CI – Confidence Interval
DVT - Deep Vein Thrombosis
IF - Impact Factor
LMWH - Low Molecular Weight Heparin
NOACs - Novel Oral Anticoagulants
PE - Pulmonary Embolism
RTC - Randomizes Controlled Trial
VTE - Venous Thromboembolism

2. Abstract

Introduction: Etiology of thrombosis is based on Virchow triad (hypercoagulability, vascular damage, circulatory stasis). In cancer all three aspects of Virchow triangle could be met. Therefore, anticoagulant drugs are used for prevention of thrombosis in cancer patients.

Purpose: RCTs have a high level of evidence in modern medicine. This study aimed at evaluating the reporting quality of RCTs on anticoagulant drugs for thromboprophylaxis in cancer patients the last 5 years (between May 2017 and May 2022) using the CONSORT statement.

Methods: Pubmed and Cochrane were used as free search engines. We searched for RTCs in English, published between May 2017 and May 2022. Quality of reporting was assessed using the CONSORT checklist, which consists of 25 items. Data analysis was performed using SPSS Statistics v26 package.

Results: Nineteen studies were evaluated as eligible. The average CONSORT compliance score was 65.78%, 95% CI (55.5%-76%). Only four studies (all published in journals that are endorsers of CONSORT statement) had CONSORT compliance >75%. A percentage of 52.63% of the studies were published in a journal that was endorsed with the CONSORT 2010. Seven of the nineteen studies were published in a journal with IF>10.

Conclusion: Quality of reporting in RCTs for anticoagulant drugs for thromboprophylaxis in cancer patients was found to be inadequate. The CONSORT statement should be widely used when reporting on RCTs.

Key words: Randomized Control Trials (RTCs), CONSORT, quality, anticoagulant drugs, cancer, thromboprophylaxis, thrombosis prevention, thrombosis, venous thromboembolism (VTE), pulmonary embolism (PE), deep vein thrombosis (DVT)

2. Περίληψη

Εισαγωγή: Η αιτιολογία της θρόμβωσης βασίζεται στην τριάδα Virchow (υπερπηκτικότητα, αγγειακή βλάβη, στάση της ροής του αίματος). Στον καρκίνο και οι τρεις πτυχές του τριγώνου Virchow θα μπορούσαν να ικανοποιηθούν. Ως εκ τούτου, τα αντιπηκτικά φάρμακα χρησιμοποιούνται για την πρόληψη της θρόμβωσης σε ασθενείς με καρκίνο.

Στόχοι: Οι RTCs έχουν μεγάλο βαθμό αποδεικτικής ικανότητας στη σύγχρονη ιατρική. Η μελέτη στόχευσε στην αξιολόγηση της ποιότητας αναφοράς των RCTs για τα αντιπηκτικά φάρμακα για θρομβοπροφύλαξη σε ασθενείς με καρκίνο τα τελευταία 5 χρόνια (μεταξύ Μαΐου 2017 και Μαΐου 2022) χρησιμοποιώντας τη δήλωση CONSORT.

Μέθοδοι: Το Pubmed και η Cochrane χρησιμοποιήθηκαν ως δωρεάν μηχανές αναζήτησης. Αναζητήσαμε RTCs στα Αγγλικά, που δημοσιεύτηκαν μεταξύ Μαΐου 2017 και Μαΐου 2022. Η ποιότητα των αναφορών αξιολογήθηκε χρησιμοποιώντας τη λίστα ελέγχου CONSORT, η οποία αποτελείται από 25 στοιχεία. Η στατιστική ανάλυση των δεδομένων πραγματοποιήθηκε με τη βοήθεια του SPSS v26.

Αποτελέσματα: Δεκαεννιά μελέτες αξιολογήθηκαν ως επιλέξιμες. Η μέση συμμόρφωση με τη δήλωση CONSORT ήταν 65.78 % CI (55.5%-76%). Μόνο τέσσερις μελέτες (όλες δημοσιευμένες σε περιοδικά που ενστερνίζονταν τη δήλωση CONSORT) είχαν συμμόρφωση με τη δήλωση CONSORT >75%. Ποσοστό 52,63% των μελετών δημοσιεύτηκε σε ένα περιοδικό που ενστερνιζόταν το CONSORT 2010. Επτά από τις δεκαεννέα μελέτες δημοσιεύτηκαν σε περιοδικό με IF>10.

Συμπέρασμα: Η αξιολόγηση της ποιότητας αναφορά των RCTs για τα αντιπηκτικά φάρμακα για θρομβοπροφύλαξη σε ασθενείς με καρκίνο βρέθηκε να είναι ανεπαρκής. Η δήλωση CONSORT θα πρέπει να χρησιμοποιείται ευρέως κατά την αναφορά σε RCT.

Λέξεις κλειδιά: τυχαιοποιημένες κλινικές δοκιμές, CONSORT, ποιότητα, αντιπηκτικά φάρμακα, καρκίνος, θρομβοπροφύλαξη, πρόληψη θρομβώσεων, θρόμβωση, θρομβοεμβολικό επεισόδιο, πνευμονική εμβολή, εν τω βάθει φλεβοθρόμβωση

3. Introduction

Nowadays the clinician is faced with plenty of questions and he should make clinical decisions. A tool that helps is RCTs that offer a high level of evidence. However, many RTCs present deficiencies in methodology, such as in the randomization or the statistical analysis [1]. The need was created for a protocol which would assess the reporting quality of RTCs. Therefore, the CONSORT (Consolidated Standards of Reporting Trials) statement was developed. It has been published in 1996 and has been revised twice, in 2001 and 2010. [2,3]

There are many RTCs that deal with anticoagulant drugs for thromboprophylaxis in cancer patients, because a significant percentage of cancer patients develop venous thromboembolism (VTE). VTE means that a blood clot is formed in a vein. There are two types of VTE which are deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is the condition in which a blood clot is formed in a deep vein mainly of the leg or arm. When this blood clot detaches from the vein wall and reaches the lungs vessels this is called PE. PE could be lethal [4].

In order a VTE to exist some factors are thought to contribute. In other words the Virchow triad that is named after the German physician Rudolf Virchow (1821-1902) is necessary. It consists of three factors: hypercoagulability, vascular damage and circulatory stasis. Hypercoagulability is an abnormal situation in blood coagulation due to congenital (overactivity of coagulation factors or deficiency of natural anticoagulants) or acquired parameters (diseases such as antiphospholipid syndrome, cancer). Vascular damage to endothelium of the vein could be caused because of implanted medical devices or trauma. Circulatory stasis happens when the blood flow is belated for example in long periods of immobility due to hospitalization, an orthopedic surgery or a long-distance travel.

In cancer all three aspects of Virchow triangle could be met. Hypercoagulability could happen because of the tumor secretion of procoagulant factors or hormonal therapy. Vascular damage could be

caused by chemotherapy or radiation therapy. Circulatory stasis could be the result of a long period immobilization of a cancer patient or an endoluminal tumor growth. Therefore, anticoagulant drugs are used for prevention of thrombosis in cancer patients.[5] The anticoagulant drugs that are used are oral (warfarin, apixaban, rivaroxaban, dabigatran, edoxaban) and by subcutaneous injection (Low Molecular Weight Heparin).[6]

This study aims at evaluating the reporting quality of RCTs on anticoagulant drugs for thromboprophylaxis in cancer patients the last 5 years (between May 2017 and May 2022) using the CONSORT statement.

4. Methods

4.1. Search Strategies

Pubmed was used as a free search engine accessing the MEDLINE database. Cochrane was also used as a free search engine. We have searched for RTCs published between May 2017 and May 2022 in Pubmed and Cochrane. The population that was included in these RTCs was cancer patients. The algorithm that we searched for was:

((CANCER* OR NEOPLASM*) AND (ANTICOAGULANT* OR NOAC* OR APIXABAN OR RIVAROXABAN OR DABIGATRAN OR EDOXABAN OR ACENOCOUMAROL OR LMWH OR HEPARIN) AND (THROMBOPROPHYLAXIS OR THROMBOSIS PREVENTION OR VTE OR DVT OR PE OR VENOUS THROMBOEMBOLISM OR DEEP VEIN THROMBOSIS OR PULMONARY EMBOLISM))

4.2. Eligibility criteria

The trials that were characterized eligible should fulfill some criteria. That's why the following filters have been used in Pubmed: RCTs (the randomization should have been done in at least two arms), in humans (cancer patients), in English language, published between May 2017 and May 2022 (the last 5 years), with free full access. The results were last updated on May 31st 2022. Observational studies, reviews, pilot studies, pooled analyses, sub-group analyses and meta-analyses of RCTS were not included.

4.3. Data extraction

The reporting quality was assessed using the revised 2010 CONSORT statement, which is a checklist that consists of 25 items (37 items if we count a and b). These items evaluate the following parts of the RCTs: 2 items the Title and Abstract, 2 items the Introduction, 17 items the Methods, 10 items the Results, 3 items the Discussion and 3 items Other information. It is listed in the Appendix (Table 3). An item was counted as sufficient and was rated with 1, when the appropriate information was found at the corresponding part of the RCT according to the 2010 CONSORT checklist. An item was counted as insufficient and was rated with 0, when the appropriate information wasn't lucid, was oracular or wasn't found at the corresponding part of the RCT. The evaluation was performed according to the article CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials.

4.4. Statistical Analysis

We evaluated the CONSORT items in the 19 RCTs by using Microsoft Excel 2007. Every item of every RCT was rated with 0 or 1. The sum of the rates of each RCT was calculated (maximum sum is 37). Afterwards the % percentage of compliance with the CONSORT statement was

calculated. Percentage 75% was decided as a cutoff of the reporting quality of each RCT as it was found suitable in many other studies.

There are currently 585 journals that approve CONSORT. The RCTs have been divided into two groups. On the one hand there are the RCTs that have been published in journals that endorse CONSORT and support the completion of the 2010 CONSORT Checklist before the publication. On the other hand there are the RCTs that consider that is not necessary to endorse the CONSORT statement. A nonparametric Mann Whitney U test and Fisher's Exact test has been applied for these two groups.

The IF is a scale that measures the influence factor of the journals in which the articles were published. Journal IF was accessed through the Academic Accelerator website.

All statistical analyses were made using the IBM SPSS Statistics v.26 package. The cutoff point for statistical significance was set at the 0.05 ($p<0,05$). The web search, the evaluation and the statistical analysis were performed by the author (K.F.).

5. Results

The initial references after the searching of our algorithm in Pubmed and Cochrane were 6823. Four hundred fifty one RCTs have remained by using the filters that we have already mentioned. We have screened these RCTs by title, by abstract and by full text [7-30]. Nineteen RCTs (Table 4) have remained as eligible. (Figure 1)

Then we studied the characteristics of each one of the nineteen eligible studies. Two (10.53%) were published in 2022, 1 (5.26%) in 2021, 7 (36.85%) in 2020, 4 (21.05%) in 2019, 4 (21.05%) in 2018 and 1 (5.26%) in 2017. A percentage of 52.63% of the studies were published in a journal that was endorsed with the CONSORT 2010. Seven of the nineteen studies were published in a journal with IF>10. (Table 1)

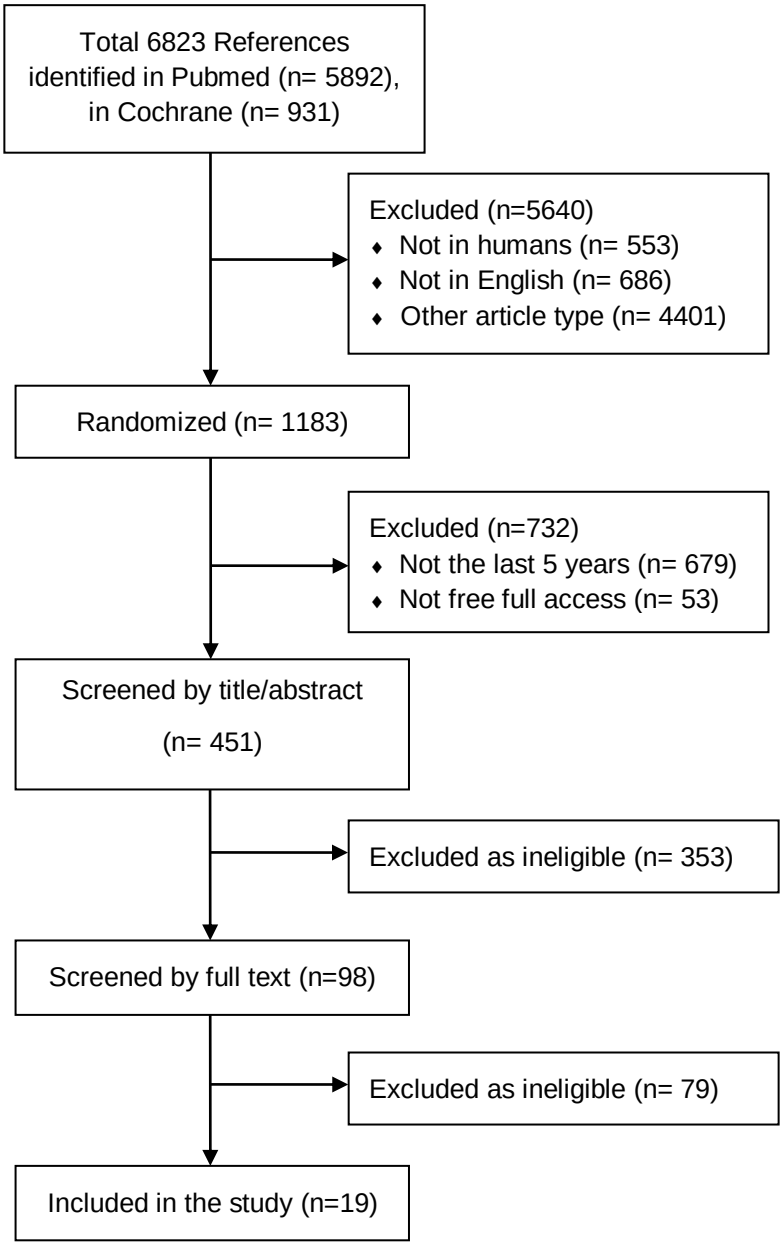

Figure 1.Flow Chart of search strategy till the eligible studies were found

The average CONSORT compliance score was 65.78 %, 95% CI (55.5 %-76 %). Only four studies (all published in journals that are endorsers of CONSORT statement) had CONSORT compliance >75%. Two of these 4 studies were published in 2020, one in 2019 and 1 in 2017.

Studies	Journal of Publication	Impact Factor	Endorser of CONSORT
Wang 2022	Medical Science Monitor	2.649	NO
Becattini 2022	Blood	22.113	YES
A-Lai 2021	BMC Surgery	1.828	YES
Yu 2020	Medicine (Baltimore)	1.740	NO
Guntupalli 2020	JAMA Network Open	8.483	NO
Zwicker 2020	Blood Advances	5.486	NO
Obitsu 2020	Journal of American College of Surgeons	6.113	NO
Orvain 2020	Blood	22.113	YES
Kamachi 2020	BJS Open	3.670	YES
Patel 2020	European Urology	20.096	YES
Carrier 2019	New England Journal of Medicine	91.245	YES
Khorana 2019	New England Journal of Medicine	91.245	YES
Tanaka 2019	Anticancer Research	2.480	NO
Hata 2019	Annals of Gastrenterological Surgery	3.452	NO
Ek 2018	Annals of Oncology	32.976	YES
Jung 2018	JAMA Surgery	14.766	YES
Dong 2018	Journal of Thoracic Disease	2.891	NO
Wang 2018	European Review for Medical and Pharmacological Sciences	3.507	NO
Christensen 2017	PLoS ONE	3.240	YES

Table 1. Characteristics of the nineteen eligible RCTs.

We tried to correlate the compliance of the RCTs with the CONSORT Checklist with the CONSORT endorsement of the journals that they have been published. The mean CONSORT compliance score of journals-endorsers of the CONSORT statement was 71.35 %, 95% CI (60.9 %-81.8 %). For the journals non-endorsers it was 59.51 %, 95% CI (48.7 %- 70.4 %). A Mann-Whitney U test has been applied. However statistically significant correlation was not proved. (p-value >0.05) (Table 2). We also used Fisher's exact test to compare each one of the 37 items between the endorsers and non-endorsers of CONCORT.

Some CONSORT items 3b, 6b, 7b, 9, 11b, 14b, 21 and 21 were absent in most of the 19 studies. It was important that all studies had a structured summary, scientific background, explanation of rationale, specific objectives and hypothesis.

CONSORT Items	Total (n=19)	Endorsers of CONSORT (n=10)	Non Endosers of CONSORT (n=9)
Title/ Abstract			
1a	0,58	0,60	0,56
1b	1,00	1,00	1,00
Introduction			
2a	1,00	1,00	1,00
2b	1,00	1,00	1,00
Methods			
3a	0,84	0,80	0,89
3b	0,05	0,10	0,00
4a	1,00	1,00	1,00
4b	0,95	1,00	0,89
5	0,95	1,00	0,89
6a	0,89	1,00	0,78
6b	0,11	0,10	0,11
7a	0,49	0,50	0,44
7b	0,37	0,60	0,11
8a	0,95	1,00	0,89
8b	0,47	0,60	0,33
9	0,32	0,50	0,11
10	0,42	0,40	0,44
11a	0,42	0,30	0,56
11b	0,05	0,00	0,11
12a	0,95	0,90	1,00
12b	0,47	0,70	0,22
Results			
13a	0,74	0,80	0,67
13b	0,84	1,00	0,67
14a	0,79	0,90	0,67
14b	0,16	0,20	0,11
15	0,95	0,90	1,00
16	0,89	1,00	0,78
17a	1,00	1,00	1,00
17b	0,63	0,70	0,56
18	0,53	0,70	0,33
19	0,84	1,00	0,67
Discussion			
20	0,84	0,90	0,78
21	0,11	0,20	0,00
22	0,95	1,00	0,89
Other information			
23	0,89	1,00	0,78
24	0,11	0,10	0,11
25	0,79	0,90	0,67

Table 2. Proportion of studies that use CONSORT statement in every item between endorses and non endorsers of CONSORT in the eligible studies (Mann-Whitney U test, p-value>0.05)

6. Conclusion

The quality of reporting in RCTs for anticoagulant drugs for thromboprophylaxis in cancer patients was found to be inadequate. The average CONSORT compliance score was 65.78 %. Only four studies had CONSORT compliance >75%. Some CONSORT items 3b, 6b, 7b, 9, 11b, 14b, 21 and 21 were absent in most of the 19 studies. However, 52.63% of the studies were published in a journal that was endorsed with the CONSORT 2010.

In the study of Liampas et al. [31] the relationship between NOACs as drugs of prevention and treatment of thromboses in cancer patients and CONSORT compliance has been analysed. It concludes that the quality of the analysing RCTs is moderate.

Our study had some limitations. First of all the data extraction and analysis was performed by one reviewer. The studies that we have searched for as eligible were in English language. So, there might be studies in other languages that could be useful about the thromboprophylaxis in cancer patients. Moreover, most of the studies (13/19) dealt with the thromboprophylaxis in cancer patients in correlation with surgery for their disease. Also, the results of some of the 19 trials could not be generalized (e.g. Korean patients were assigned, the sample size was small). Last but not least, we should mention that there were some adverse events in the RCTs that we have analysed such as bleeding or elevation of liver enzymes due to the use of anticoagulant drugs. These adverse events should be analysed further.

In summary, the CONSORT statement should be widely used when reporting on RCTs. Further study and analysis is needed to find which cancer patients are the most suitable for the use of anticoagulant agents as thromboprophylaxis.

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8. Appendix

Table 3.CONSORT 2010 checklist of information to include when reporting a RCT

Section/Topic	Item No	Checklist item
Title and abstract	1a	Identification as a randomised trial in the title
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)
Introduction	2a	Scientific background and explanation of rationale
Background and objectives	2b	Specific objectives or hypotheses
Methods		
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons
Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed
	6b	Any changes to trial outcomes after the trial commenced, with reasons
Sample size	7a	How sample size was determined
	7b	When applicable, explanation of any interim analyses and stopping guidelines
Randomisation:		
Sequence generation	8a	Method used to generate the random allocation sequence
	8b	Type of randomisation; details of any restriction (such as blocking and block size)
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how
	11b	If relevant, description of the similarity of interventions
Statistical methods	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		
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome
	13b	For each group, losses and exclusions after randomisation, together with reasons
Recruitment	14a	Dates defining the periods of recruitment and follow-up
	14b	Why the trial ended or was stopped
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)
Discussion		
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

Generalisability	21	Generalisability (external validity, applicability) of the trial findings
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence
Other information		
Registration	23	Registration number and name of trial registry
Protocol	24	Where the full trial protocol can be accessed, if available
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders

Table 4.RCTs eligible for the analysis (19 in total)

1. Wang ZY, Wan YD, Liu XZ, Wang H, Jiang GY, Yang B. **A Single-Center, Randomized, Double-Blind Study of 94 Patients Undergoing Surgery for Cerebral Glioma to Compare Postoperative Thromboprophylaxis with and without Rivaroxaban**. Med Sci Monit. 2022 Feb 10;28:e934341. doi: 10.12659/MSM.934341. PMID: 35140195; PMCID: PMC8845378.

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