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CLINICAL STUDY

Venous thromboembolism prophylaxis in brain tumor patients undergoing craniotomy: a meta-analysis

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Abstract Brain tumor patients undergoing craniotomy generally receive prophylaxis against venous thromboembolism (VTE), but modalities in use differ widely and have been debated in the literature. A systematic review and meta-analysis was conducted to assess the efficacy and safety of VTE prophylaxis among brain tumor patients undergoing craniotomy. Ten randomized controlled trials were included in the final efficacy analysis. The various prophylactic measures employed in these studies reduced the risk for thrombosis compared to controls with an overall risk ratio of 0.61 (95 % CI: 0.47–0.79) in the fixed effect model. Although Cochrane Q-test showed unimportant heterogeneity across studies ($p = 0.19$) and the I^2, a measure of heterogeneity between studies, was reasonably low at 28 %, subgroup analysis indicated that intervention type was a potential effect modifier for efficacy ($p = 0.04$). Unfractionated heparin alone showed a stronger reduction in VTE risk compared to placebo (RR = 0.27; 95 % CI: 0.10–0.73), and LMWH combined with mechanical prophylaxis showed a lower VTE risk as compared to mechanical prophylaxis alone (0.61; 95 % CI: 0.46–0.82). This meta-analysis demonstrates a statistically significant VTE risk reduction among brain tumor patients receiving prophylaxis, with chemical prophylaxis showing the strongest risk reduction. Five studies were included in the safety analysis, which showed an overall increased risk of bleeding comparing different prophylactic measures to different controls (RR = 2.02; 95 % CI: 1.14–3.58; $I^2 = 0$ %; $p = 0.86$). Interventions in these studies were associated with an increased risk of post-operative, minor hemorrhage (RR = 2.20; 95 % CI = 1.00; 4.85), while the risk of major hemorrhage was not increased by chemoprophylaxis.

Introduction

Patients with brain tumors undergoing craniotomy are at a significantly increased risk of developing venous thromboembolism (VTE). Previously reported risks for developing deep vein thrombosis (DVT) and pulmonary embolism (PE) are 31 and 5 %, respectively, for patients undergoing craniotomy [1–3]. The etiology of these events is multifactorial and includes relative stasis after surgery, direct activation of the coagulation cascade due to tissue damage, as well as tumor-specific pro-coagulant effects. Other risk factors include older age, large tumor size, and peri-operative steroid use. Injury to the vessel wall due to chemotherapy and/or radiation therapy can further increase the risk of VTE among brain tumor patients [4–7].

Interventions used to prevent VTE in brain tumor patients undergoing craniotomy include mechanical prophylaxis and/or pharmacological prophylaxis. Current modalities for mechanical prophylaxis include the application of sequential

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compression devices (SCD), graduated compression stockings, or a combination of both [8]. Pharmacological prophylaxis is typically achieved with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), which reduce the incidence of VTE through direct anticoagulation effects but also carry the risk of postoperative bleeding [9, 10].

The American College of Chest Physicians' (ACCP) guidelines consider patients with central nervous system neoplasms undergoing surgery a high-risk population for VTE and recommend both pharmacologic prophylaxis and mechanical prophylaxis. The exact methods and timing for commencing pharmacological prophylaxis were not specified, however [11]. The National Institute for Health and Care Excellence (NICE) guidelines recommend mechanical prophylaxis among all neurosurgical patients, but recommend pharmacological prophylaxis only among patients who are considered low risk for hemorrhage [12].

In this systematic review and meta-analysis, randomized controlled trials (RCTs) that evaluated the efficacy and safety of different methods of prophylaxis in brain tumor patients undergoing craniotomy were pooled for analysis. We aim to help guide clinical practice for these patients by identifying the most efficacious and safest modality for VTE prophylaxis.

Methods

Literature search

The PubMed, EMBASE, and Cochrane Library databases were searched from their establishment date through October 2014 for studies evaluating the efficacy and safety of pharmacological prophylaxis and/or mechanical prophylaxis in brain tumor patients undergoing craniotomy. An additional supplementary search was performed at the time of manuscript review, through June 30, 2016. Appropriate medical subject heading (MeSH) terms, text words (tw), and Emtree terms were used (Appendix 1). Additional articles were identified from the reference lists of relevant studies and reviews.

Study selection

Studies were included if they met the following criteria: (1) RCTs conducted on patients diagnosed with brain tumor and undergoing craniotomy, (2) patients were older than 18 years old, recently diagnosed with a brain tumor of any grade, not at risk of VTE and without a history of VTE events, and who were randomly assigned to prophylaxis (chemical prophylaxis, mechanical prophylaxis, or a combination of both),

(3) sample size of greater than or equal to 20 patients with reported data on efficacy outcomes (e.g., symptomatic and objectively verified VTE) or safety outcomes (e.g., major or minor hemorrhage). Articles were excluded if they were not in English. Titles and abstracts were screened and potentially relevant articles were selected for full-text evaluation, which was performed independently by five investigators. Discrepancies were resolved by consultation with the senior authors (R.A.M., T.R.S.). The quality of the RCTs was evaluated using the Jadad score, which assesses randomization, double blinding, and withdrawals/dropouts on a scale from zero (very poor) to five (rigorous) [12].

Data extraction

For each identified article, the following information was extracted: study characteristics (authors, publication year, country of origin, sample size, number included for intent-to-treat analysis, center type, number of surgeons, follow-up duration, journal impact factor); participant characteristics (gender, age, ethnicity, inclusion/exclusion criteria, types of tumor, comorbidities), perioperative details, VTE intervention details (dose, duration, frequency, administration time), study control type, efficacy outcomes (number of VTE events in each group), and safety outcomes (occurrence of bleeding, hemorrhage, or any other adverse event). Data extraction was conducted independently by two investigators.

Data analysis

Data analysis was performed using Comprehensive Meta-Analysis (CMA) Version 3 (Biostat, Inc., Englewood, NJ, USA). The fixed-effects model using the inverse variance method was used to obtain the overall relative risk (RR) estimates and the 95 % confidence intervals for both the efficacy and safety analyses. A random-effects model according to the method of DerSimonian and Laird [13] that accounted for variation between studies in addition to within-study variance was evaluated for comparison. Forest plots were used to visualize the individual and summary estimates. Heterogeneity was evaluated among studies by using the Cochran's Q-test ($p < 0.10$) and the I^2 to measure the proportion of total variation due to that heterogeneity. An I^2 value >50 % was considered to be high [14]. Potential sources of heterogeneity were explored using sub-group analyses by categorical covariates [intervention type (chemical vs. chemical; chemical vs. mechanical; chemical vs. placebo; and mechanical vs. placebo), follow-up duration (≤30 days; >30 days; N/A), intervention time (preoperative; postoperative), study quality (≤3; >3), center type (multicenter; single), and region of study origin (US; non-US)]. Studies that classified prophylaxis as preoperative and/or perioperative

were grouped in one category. A univariate meta-regression was conducted on each categorical covariate separately as well as on age (continuous) and a multivariate meta-regression was also used to explore sources of heterogeneity. A sensitivity analysis was conducted to examine the influence of individual studies on the overall risk estimate by recalculating the pooled estimates for the remainder of the studies after removing one study at a time. A cumulative meta-analysis was conducting by publication year. Potential publication bias was assessed by funnel plots, Egger's linear regression test, and Begg's correlation test. If publication bias was indicated, the number of missing studies was evaluated by the trim and fill method. A p-value <0.05 was considered significant unless otherwise indicated. Because Peto's method [15] using the hypergeometric variance performs well with low-rate events ($\leq 1\%$), all of the above models using were recalculated using Peto odds ratio (OR) estimates.

Results

Study characteristics

After the systematic search, 826 articles from PubMed, 226 articles from Embase, and eight articles from the Cochrane Library were identified (Fig. 1). After the removal of duplicates and papers that did not meet the inclusion criteria based on title and abstract, 33 articles remained for full text review. After the final review, ten RCTs reporting 212 VTE events among 1263 participants were included in this meta-analysis [1–6, 9, 16–18]. No RCTs meeting the inclusion criteria were identified in the supplementary search performed at the time of review, through June 30, 2016.

Characteristics of the ten RCTs included in this meta-analysis are found in Table 1. In the intervention arm, the total number of participants ranged from 11 to 193 and the number of VTE cases from 1 to 33. In the control arm, the

Fig. 1 Study selection process of the identified articles
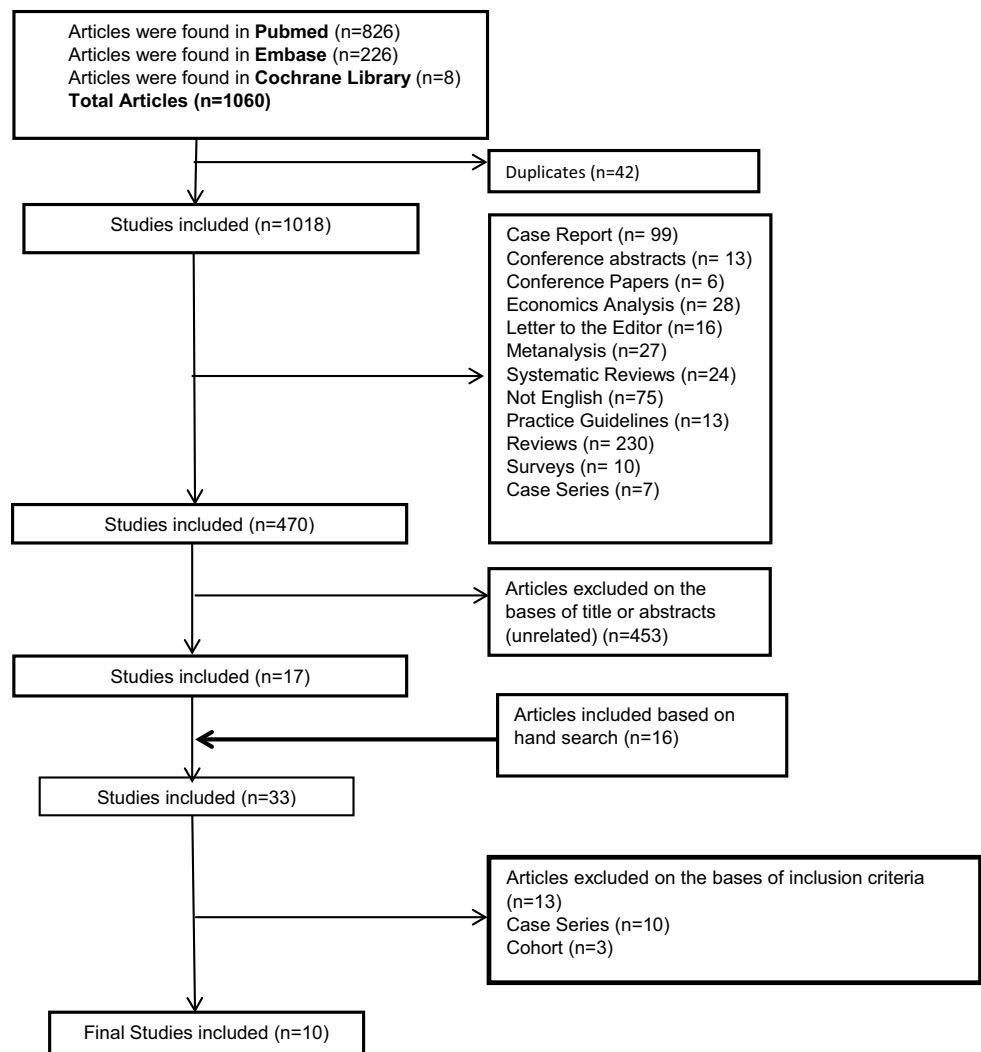
Table 1 Characteristics of the 10 clinical trials included in the meta-analysis

Study year	Time of prophylaxis initiation	Single or multi center	Number included for analysis (ITT)[a]	Type of intervention (name, dose and frequency)	Control type	Follow-up duration	Country	JADAD score	Inter-vention arm n/N	Control arm n/N
Agnelli, G. 1998 [4]	Post	Multi	307	Enoxaparin 40 mg SC once daily+thigh-length compression stocking	Placebo+thigh length compression stocking fitted on the morning of surgery until discharge	60 days	US	4	22/130	43/130
Bucci, M. N. 1989 [18]	Pre	Single	70	Anti-embolism stockings	IPC	N/A	US	1	1/32	1/38
Cerrato, D. 1978 [19]	Pre	Single	100	Heparin calcium 5000 U SC	No chemoprophylaxis	N/A	US	2	3/50	17/50
Constantini, S. 2001 [5]	Pre	Single	103	5000 U heparin SC/12 HRS	Placebo (0.9% NaCl alone)	N/A	Israel	5	2/55	2/48
Dickinson, L. D. 1998 [2]	Pre	Single	68	Enoxaparin 30 ml SC/12 h + sequential compression device (SCD)	SCD	30 days	US	1	3/22	4/23
Goldhaber, S. Z. 2002 [3]	Post	Single	150	Enoxaparin, 40 mg SC AM+placebo injection SC PM+mechanical (GCS AND IPC)	Heparin 5000 U+mechanical (GCS AND IPC)	30 days	US	5	9/71	5/68
Macdonald, R. L. 2003 [6]	Peri	Single	100	Dalteparin, 2,500 units once a day+mechanical IPC	Heparin 5000 U/12 HRS+mechanical (GCS AND IPC)	30 days	US	4	1/35	0/28
Nurmohamed, M. 1996 [9]	Post	Multi	485	Nadroparin calcium, 7500 sq once daily+mechanical GCS	Placebo+mechanical (GCS AND IPC)	56 days	Germany	2	33/193	51/207
Skillman, J. J. 1978 [17]	Peri	single	95	Mechanical prophylaxis (EPC)	No prophylaxis	Until discharge (study duration not available)	US	2	1/11	7/20
Turpie, A. G. 1977 [16]	Post	Single	128	IPC to the calves	No prophylaxis other than routine physiotherapy	5–14 days	Canada	2	1/25	6/27

ITT intent-to-treat, *SC* subcutaneous, *U* unit, *GCS* graduated compression stockings, *IPC* intermittent pneumatic compression, *SCD* sequential compression device, *N/A* no information was provided; this was considered as a placebo in the subgroup analysis by intervention type

[a] The ITT column represents the number of participants reported by the study; only participants who met the inclusion criteria of our meta-analysis were included in the calculation of the RR

total number of participants ranged from 20 to 207 and the number of VTE cases from 0 to 51. All studies included both men and women but only seven of ten studies gave the exact percentage of men and women per study. For those studies, the male percentage ranged from 45 to 52% in the intervention arm and from 44 to 58% in the control arm.

The mean age of participants ranged from 49 to 57.5 years. Seven studies were conducted in the United States (US), one in Israel, one in Germany, and one in Canada. Study follow-up varied across studies (5–348 days). VTE prophylaxis was started either pre/perioperatively (six studies) [2, 5, 17–20] or postoperatively (four studies) [3, 9, 16, 21]. The types of prophylaxis used in each study were diverse and were compared to different controls.

Assessment of study quality using the Jadad score yielded an average score of 2.8. The diagnosis and reporting of VTE varied across the RCTs. In all studies except for one [5], asymptomatic VTE was diagnosed by using an ultrasound or a venography during the post-operative period prior to discharge. The study publication year started as early as 1977 and the most recent study was in 2003. Trials that did not report details about the type of control were considered compared to placebo. The analyses conducted on the ten RCTs as well as in our meta-analysis were done on the intent-to-treat population.
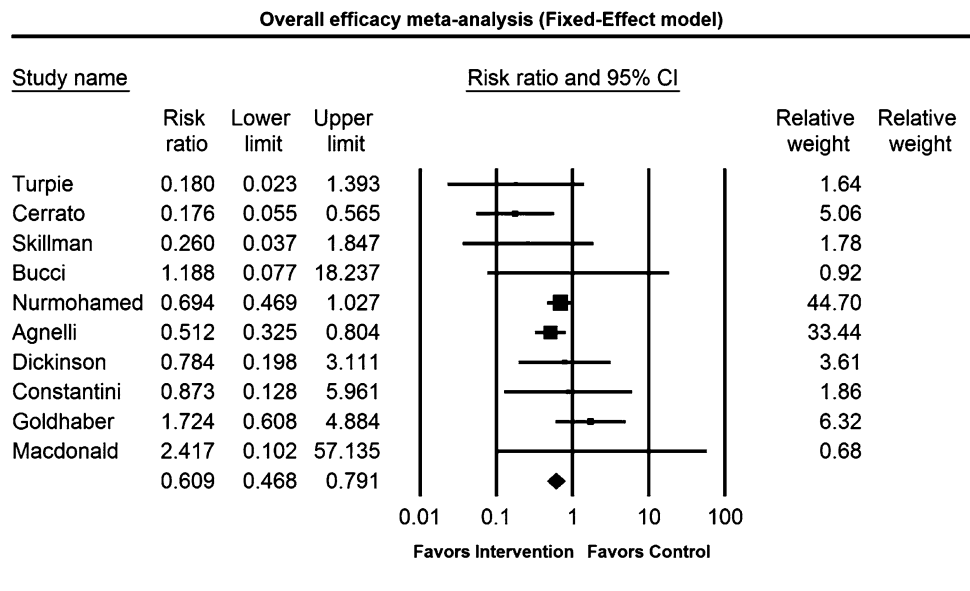
Efficacy analysis

Of the ten studies included in the meta-analysis, only two demonstrated a significant reduction in VTE risk [1, 4]; one study was borderline significant [9]; while the remaining seven trials reported non-statistically significant results.

Pooling results from all ten studies demonstrated a protective effect between the different prophylaxis regimens and VTE risk (Fig. 2). The pooled RR of VTE was 0.61 (95% CI: 0.47; 0.79; fixed-effects model). Results from the random-effects model were similar (0.60; 95% CI: 0.40; 0.89) and no significant heterogeneity was observed ($I^2 = 28\%$; P-heterogeneity = 0.19).

Subgroup analyses revealed that intervention type was a potential effect modifier (p = 0.04). Specifically, UFH alone showed a stronger reduction in VTE risk as compared to placebo (RR = 0.27; 95% CI: 0.10–0.73), while LMWH combined with mechanical prophylaxis showed a lower VTE risk as compared to mechanical prophylaxis alone (RR = 0.61; 95% CI: 0.46–0.82). The remaining comparisons (combination of LMWH and mechanical prophylaxis vs. combination of UFH and mechanical prophylaxis; mechanical prophylaxis vs. placebo) showed non-significant results (Fig. 3). Using the Peto OR for the comparison of mechanical prophylaxis vs. placebo revealed a significant reduction in VTE events (Peto OR = 0.30; 95% CI = 0.11; 0.87). Subgroup analysis and meta-regression analyses based on other trial-level covariates such as age (p = 0.24), intervention time (p = 0.74), follow-up duration (p = 0.15), study quality (p = 0.67), center type (p = 0.98), and country (p = 0.98) showed no significant evidence that effects varied by group. Dose was not tested for effect modification because of the diversity of the interventions used in these trials.

A multi-covariate meta-regression model adjusting for all the previous variables did not explain significant between-study variance (overall p = 0.38). A symmetrical inverted funnel plot suggested the absence of publication bias along

Fig. 2 Forest plot represents the relative risk for developing venous thromboembolism (VTE) (95% CI) with different prophylactic regimens as compared to different control regimens from ten randomized controlled studies in adult brain tumor patients undergoing craniotomy. *Horizontal lines* denote 95% CIs, *solid squares* represent the point estimate of each study and the *diamond* represents the pooled estimate of the intervention effect. The size of the *solid squares* is proportional to the weight of the study. Weights are from the fixed-effects analysis using the using the inverse variance method. The I^2 and p values for heterogeneity are shown

Overall efficacy meta-analysis (Fixed-Effect model)

Study name	Risk ratio	Lower limit	Upper limit	Risk ratio and 95% CI	Relative weight
Turpie	0.180	0.023	1.393		1.64
Cerrato	0.176	0.055	0.565		5.06
Skillman	0.260	0.037	1.847		1.78
Bucci	1.188	0.077	18.237		0.92
Nurmohamed	0.694	0.469	1.027		44.70
Agnelli	0.512	0.325	0.804		33.44
Dickinson	0.784	0.198	3.111		3.61
Constantini	0.873	0.128	5.961		1.86
Goldhaber	1.724	0.608	4.884		6.32
Macdonald	2.417	0.102	57.135		0.68
	0.609	0.468	0.791		

Favors Intervention   Favors Control

I-squared= 28%, P= 0.19

Efficacy sub-group analysis by intervention type (Fixed-Effect model)

Group by Type of Intervention	Study name	Risk ratio	Lower limit	Upper limit	Risk ratio and 95% CI
Anticoagulant (UFH) vs Placebo	Cerrato	0.176	0.055	0.565	
Anticoagulant (UFH) vs Placebo	Constantini	0.873	0.128	5.961	
Anticoagulant (UFH) vs Placebo		0.271	0.100	0.733	
Comb. (LMWH) vs Comb. (UFH)	Goldhaber	1.724	0.608	4.884	
Comb. (LMWH) vs Comb. (UFH)	Macdonald	2.417	0.102	57.135	
Comb. (LMWH) vs Comb. (UFH)		1.782	0.663	4.791	
Comb. (LMWH) vs Mechanical	Nurmohamed	0.694	0.469	1.027	
Comb. (LMWH) vs Mechanical	Agnelli	0.512	0.325	0.804	
Comb. (LMWH) vs Mechanical	Dickinson	0.784	0.198	3.111	
Comb. (LMWH) vs Mechanical		0.616	0.461	0.823	
Mechanical vs Placebo	Turpie	0.180	0.023	1.393	
Mechanical vs Placebo	Skillman	0.260	0.037	1.847	
Mechanical vs Placebo	Bucci	1.188	0.077	18.237	
Mechanical vs Placebo		0.312	0.089	1.097	
Overall		0.609	0.468	0.791	

0.01   0.1   1   10   100

Favors Intervention Favors Control

Fig. 3 Forest plot represents the relative risk for developing venous thromboembolism (VTE) (95 % CI) with different prophylactic regimens as compared to different control regimens from ten randomized controlled studies in adult brain tumor patients undergoing craniotomy. *Horizontal lines* denote 95 % CIs, *solid squares* represent the point estimate of each study and the *diamonds* represent the pooled estimate of the intervention effects for each subgroup. The size of the solid squares is proportional to the weight of the study. Weights are from the fixed-effects analysis using the using the inverse variance method. The first group represents the anticoagulant UFH alone as compared to placebo ($I^2 = 48.61$ %; p = 0.16); the second group represents the combination of LMWH with mechanical prophylaxis vs. combination of UFH with mechanical prophylaxis ($I^2 = 0$ %; p = 0.84); the third group represents the combination of LMWH with mechanical prophylaxis vs. mechanical prophylaxis alone ($I^2 = 0$ %; p = 0.57); the fourth group represents mechanical prophylaxis vs. placebo ($I^2 = 0$ %; p = 0.54)

Fig. 4 Efficacy funnel plot of log risk ratio according to their standard errors using the fixed-effect model. The *vertical solid line* is drawn at the pooled log risk ratio, and the other *two lines* represent the expected 95 % confidence interval for a given standard error. The *plot* shows no significant publication bias
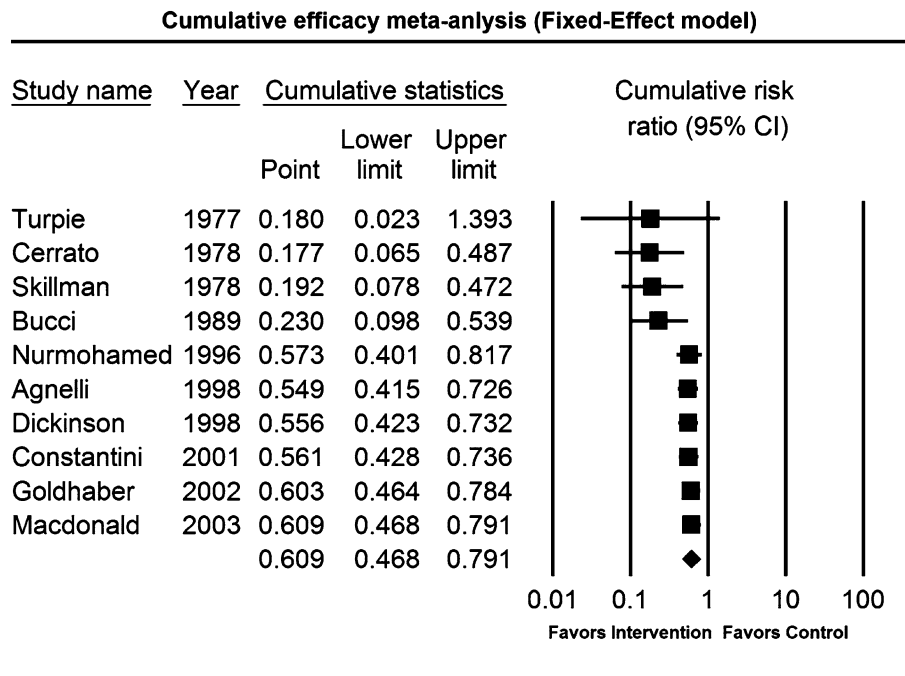

Funnel Plot of Standard Error by Log risk ratio
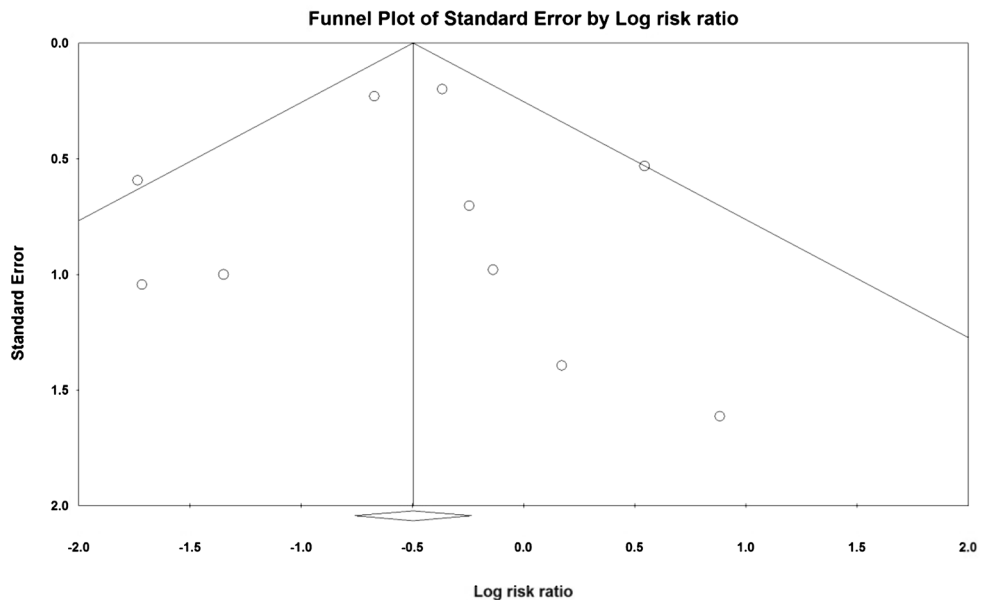
the efficacy analysis (Fig. 4). Both Begg's rank correlation test (p = 0.93) and Egger's linear regression test (p = 0.94) indicated no publication bias. The one-study removal sensitivity analysis did not change the summary estimate. The cumulative meta-analysis showed that the efficacy of the intervention was shown as early as 1978 and remained consistent until the latest study in 2003 (Fig. 5).
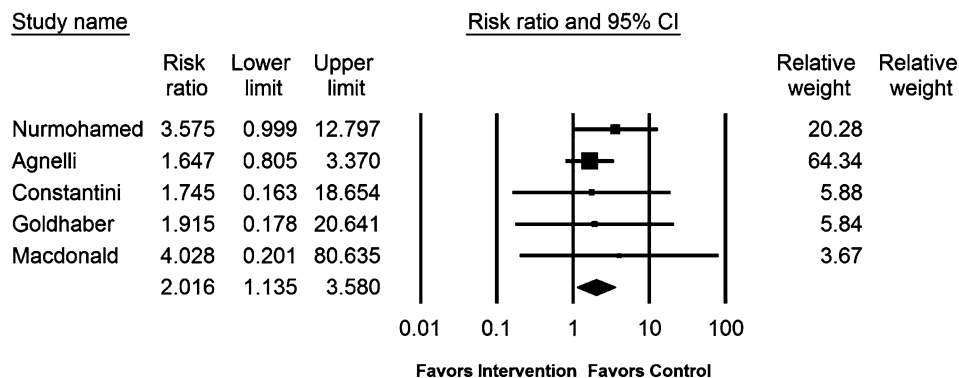
Safety analysis

Only five studies were included in the safety analysis as data pertaining to the occurrence of hemorrhage or bleeding was lacking from the remaining five studies [3–6, 9], of which only four discerned major [3, 4] from minor [4–6] bleeding. None of the five studies showed a significant increased risk

Fig. 5 Cumulative efficacy of controlled trials of different prophylactic regimens among brain tumor patients undergoing craniotomy, fixed-effect model. The data corresponds to Fig. 2. A statistically significant beneficial effect on venous thromboembolism risk became evident in 1978

Cumulative efficacy meta-analysis (Fixed-Effect model)

Study name	Year	Cumulative statistics			Cumulative risk ratio (95% CI)
		Point	Lower limit	Upper limit	
Turpie	1977	0.180	0.023	1.393	
Cerrato	1978	0.177	0.065	0.487	
Skillman	1978	0.192	0.078	0.472	
Bucci	1989	0.230	0.098	0.539	
Nurmohamed	1996	0.573	0.401	0.817	
Agnelli	1998	0.549	0.415	0.726	
Dickinson	1998	0.556	0.423	0.732	
Constantini	2001	0.561	0.428	0.736	
Goldhaber	2002	0.603	0.464	0.784	
Macdonald	2003	0.609	0.468	0.791	
		0.609	0.468	0.791	

0.01　0.1　1　10　100

Favors Intervention　Favors Control

Overall safety meta-analysis (Fixed-Effect model)

Study name	Risk ratio	Lower limit	Upper limit	Risk ratio and 95% CI	Relative weight	Relative weight
Nurmohamed	3.575	0.999	12.797		20.28	
Agnelli	1.647	0.805	3.370		64.34	
Constantini	1.745	0.163	18.654		5.88	
Goldhaber	1.915	0.178	20.641		5.84	
Macdonald	4.028	0.201	80.635		3.67	
	2.016	1.135	3.580			

0.01　0.1　1　10　100

Favors Intervention　Favors Control

I-squared= 0%, P= 0.86

Fig. 6 Forest plot represents the relative risk for developing complications (95% CI) with different prophylactic regimens as compared to different control regimens from five randomized controlled studies in adult brain tumor patients undergoing craniotomy. *Horizontal lines* denote 95% CIs, *solid squares* represent the point estimate of each study and the *diamond* represents the pooled estimate of the intervention effect. The size of the *solid squares* is proportional to the weight of the study. Weights are from the fixed-effect analysis using the using the inverse variance method. The I^2 and p values for heterogeneity are shown

of combined major/minor hemorrhagic events in the intervention group; however, pooling these study results demonstrated a significant effect between the different prophylaxis regimens and combined major/minor hemorrhagic events risk (Fig. 6). This increased risk seemed to be mostly driven by minor hemmorhages (RR = 2.20; 95 % CI = 1.00; 4.85) as the pooled OR for major hemmorhages was not significant (RR = 1.20; 95 % CI = 0.36; 3.95). The pooled RR of adverse events was 2.02 (95 % CI: 1.14; 3.58; fixed-effect

model). Results from the random-effects model were similar (RR = 2.02; 95 % CI: 1.14; 3.58) and no significant heterogeneity was observed ($I^2 = 0 \%$; P-heterogeneity = 0.86).

Subgroup analyses provided no evidence that the pooled effects varied by group for either intervention type (p = 0.96), intervention time (p = 0.90), follow-up duration (p = 0.96), study quality (p = 0.35), center (p = 0.90), or country (p = 0.40). Both the univariate meta-regression analyses on age and on each of these covariates separately

(all p values >0.05) and the multi-variate meta-regression (simultaneously adjusting for study quality and center; overall p = 0.58) did not explain significant between-study variance. Although the funnel plot did not give clear results owing to the limited number of safety studies (n = 5) (not shown), both Begg's rank correlation test (p = 0.46) and Egger's linear regression test (p = 0.42) indicated no publication bias. The one-study removal sensitivity analysis did not change the summary estimate. The cumulative meta-analysis showed that the efficacy of the intervention was shown as early as 1998 and remained consistent until the latest study in 2003. All of the above-mentioned results did not materially change with the random-effects model (not shown) or when using Peto odds ratio (not shown), except when otherwise indicated.

Discussion

Upon meta-analysis, a statistically significant decrease in VTE events with prophylaxis was found. Subgroup analysis suggested that intervention type is an effect modifier of this risk reduction. Among the studies included, UFH alone showed a stronger reduction in VTE events than placebo, followed by LMWH and mechanical prophylaxis combined, which showed a lower VTE risk than mechanical prophylaxis alone. These findings suggest that chemoprophylaxis for VTE is effective and can successfully reduce the incidence of VTE in patients undergoing craniotomy for brain tumor.

Pooled analysis also demonstrated a statistically significant increase in hemorrhagic events among patients receiving prophylaxis, although only five studies were included in this analysis. While there was a statistically significant increase in hemorrhagic events, this was driven by minor, and not major, bleeding, although only two studies reported major bleeding [3, 4]. These findings correlate with the efficacy analysis and characterize the dilemma inherent in prophylaxis for patients undergoing tumor resection: the more effective the intervention (due to its mechanism of action), the higher the chance of adverse events such as minor hemorrhage. Nevertheless, only five studies published data regarding safety of intervention, and only four of these discerned major from minor bleeding; thus, this topic would benefit from further studies.

Patients undergoing surgery of any type have repeatedly been shown to be at an increased risk of VTE, which is classically explained by Virchow's triad of hemodynamic changes, endothelial injury, and hypercoagulability [22–27]. Relative stasis post-operatively can result in procoagulative hemodynamic changes in the venous circulation, while direct tissue violation intraoperatively increases the risk of coagulation in general [28, 29]. Some tumors, such as glioblastoma multiforme, have also been shown to exert direct hypercoagulative effects through the secretion of circulating tissue factor [30, 31].

Similarly, patients undergoing craniotomy for brain tumor are considered to be at high risk for VTE, due to both the above-mentioned factors and particularly prolonged stasis as a result of long durations of general anesthesia and longer hospital stays [11, 28, 32–34]. In clinical decision making, however, these risks must be weighed against the risks of adverse events from anticoagulation, including postoperative hemorrhage. In the case of patients undergoing resection of brain tumor, the complications of hemorrhage into the tumor bed can be particularly severe, and can include permanent neurological deficit, stroke, or death [35–38]. In all cases, regardless of the findings of RCTs or meta-analyses, post-operative anticoagulation must be individualized to the patient. Nevertheless, high quality data in the form of meta-analyses regarding the relative efficacy and safety of a treatment modality across entire populations, such as post-operative anticoagulation, can help drive effective clinical practice.

To evaluate the safety and efficacy of various anticoagulation methods typically used for patients undergoing craniotomy, numerous investigators have undertaken randomized clinical trials [3, 5, 9, 16, 17, 21, 39–42]. These clinical trials have variably compared different forms of mechanical prophylaxis (e.g., stockings, SCD) and chemical prophylaxis (e.g., LMWH, UFH) against different controls.

Our specific aim was to advance the understanding of VTE prophylaxis after craniotomy for brain tumor, in terms of both efficacy and safety, by pooling together the results of these studies in a meta-analysis. Although some studies have demonstrated the efficacy of prophylaxis, others have shown no statistical difference between the tested prophylaxis modalities and controls [2, 3, 5, 9, 21, 43]. Additionally, none of the studies included in this analysis reported an increased risk of adverse events with prophylaxis. By pooling these studies together, we hoped to increase the power of the analysis, potentially discovering new findings that could inform clinical decision making surrounding the complex and nuanced issue of VTE prophylaxis in patients undergoing craniotomy for brain tumors. Interestingly, the most recent study included in this analysis was published in 2003, demonstrating a need for more up-to-date recommendations on VTE prophylaxis that we believed could be generated by detailed meta-analysis of the highest quality studies available.

Previous meta-analyses in the neurosurgical literature on VTE development and prophylaxis are relatively limited. In 2008, Collen et al. reported the results of a comprehensive meta-analysis analyzing VTE prophylaxis in all neurosurgical patients [43]. The results of their study suggested that patients undergoing craniotomy for intracranial

neoplasms may be at higher risk for VTE development, and would therefore benefit from combined therapy, a finding corroborated by the data presented here. The RR of VTE development in patients receiving prophylaxis reported in their study was similar to that reported here (0.60, 95 % CI: 0.44–0.81 vs. 0.61, 95 % CI: 0.47–0.79). This prior study was limited in that it reported higher rates of heterogeneity than those reported here, likely due to the inclusion of both RCTs and cohort studies, and did not stratify into detailed subgroup analyses by other covariates. Third, the high heterogeneity in the previous meta-analysis could be attributed to the inclusion of both RCTs and cohort studies as well as the inclusion of all neurosurgery patients; both of these issues were amended in our meta-analysis in which only RCTs including brain tumor patients undergoing craniotomy were included.

Limitations of our study include the inherent limitations of a meta-analysis, most importantly a dependence on the quality of studies pooled for analysis. In an effort to combine only the highest quality evidence, we elected to include only RCTs in this meta-analysis, excluding all cohort studies. The relatively low heterogeneity of the included studies and the lack of evidence of publication bias both support the findings of this meta-analysis. No meta-analytic conclusion could be drawn regarding the best administration time or type of the prophylaxis with respect to major bleeding, however, owing to the lack of information included in the studies analyzed. Missing data that would have been relevant in this analysis included the histologic type of tumors being treated, whether patients were undergoing index or repeat craniotomy, and the location and type of hemorrhage post-operatively. The first two of these may affect the risk of VTE post-operatively, while the latter would affect the relative safety of chemoprophylaxis in the post-operative period.

Conclusion

This meta-analysis demonstrates a statistically significant VTE risk reduction among brain tumor patients receiving prophylaxis, with chemical prophylaxis showing the strongest risk reduction. Interventions in these studies were associated with an increased risk of post-operative minor hemorrhage.

Compliance with ethical standards

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