North American Spine Society Journal (NASSJ) 17 (2024) 100295

Contents lists available at ScienceDirect

North American Spine Society Journal (NASSJ)

journal homepage: www.elsevier.com/locate/xnsj

Systematic Review/Meta-analyses

Chemical prophylaxis and venous thromboembolism following elective spinal surgery: A systematic review and meta-analysis

Roman Rahmani, DO[a], Samuel Eaddy, MS[a,*], Samuel D. Stegelmann, MD[b], Gabriel Skrobot, BS[a], Thomas Andreshak, MD[a]

[a] Mercy Health St. Vincent Medical Center, Department of Orthopedics, 2409 Cherry St, Suite #10, Toledo, OH 43608, United States
[b] HCA Medical City Healthcare UNT-TCU GME (Denton), 3535 S Interstate 35, Denton, TX 76210, United States

ARTICLE INFO

Keywords:
Thrombosis
Chemoprophylaxis
Anticoagulation
Elective
Spine surgery
Venous thromboembolism
Deep vein thrombosis
Pulmonary embolism
Spinal epidural hematoma
Thromboprophylaxis

ABSTRACT

Background: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a potentially devastating complication after surgery. Spine surgery is associated with an increased risk of postoperative bleeding, such as spinal epidural hematomas (SEH), which complicates the use of anticoagulation. Despite this dilemma, there is a lack of consensus around perioperative VTE prophylaxis. This systematic review investigates the relationship between chemoprophylaxis and the incidence rates of VTE and SEH in the elective spine surgical population.

Methods: A comprehensive literature search was performed using PubMed, Embase, and Cochrane databases to identify studies published after 2,000 that compared VTE chemoprophylaxis use in elective spine surgery. Studies involving patients aged < 18 years or with known trauma, cancer, or spinal cord injuries were excluded. Pooled incidence rates of VTE and SEH were calculated for all eligible studies, and meta-analyses were performed to assess the relationship between chemoprophylaxis and the incidences of VTE and SEH.

Results: Nineteen studies met our eligibility criteria, comprising a total of 220,932 patients. The overall pooled incidence of VTE was 3.2%, including 3.3% for DVT and 0.4% for PE. A comparison of VTE incidence between patients that did and did not receive chemoprophylaxis was not statistically significant (OR 0.97, p=.95, 95% CI 0.43–2.19). The overall pooled incidence of SEH was 0.4%, and there was also no significant difference between patients that did and did not receive chemoprophylaxis (OR 1.57, p=.06, 95% CI 0.99–2.50).

Conclusions: The use of perioperative chemoprophylaxis may not significantly alter rates of VTE or SEH in the elective spine surgery population. This review highlights the need for additional randomized controlled trials to better define the risks and benefits of specific chemoprophylactic protocols in various subpopulations of elective spine surgery.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a dangerous and potentially life-threatening complication associated with spine surgery [1]. Although VTE is a known risk, incidence rates following spinal surgery have been poorly defined, with reported rates from 0.2%-31% [2–4]. Such a wide range of incidence relates to varying degrees of risk affiliated with different types of spine surgery, with rates of DVT and PE in elective surgery being as low as 1.09% and 0.06%, respectively [5].

Given the potential for this significant complication, surgeons must weigh the benefits of VTE prophylaxis against the risks. Mechanical methods, such as external compression devices, can be used with little to no danger to the patient and are generally accepted preventive measures [6]. Research has suggested, however, that chemical anticoagulants may be even more effective at minimizing the risk of VTE [5,7]. The use of anticoagulants, however, must be balanced against the risk of bleeding complications including spinal epidural hematomas (SEH) [8]. Although SEHs are infrequent, they can cause devastating neurologic injury [9], leading many surgeons to avoid the use of anticoagulants during elective spinal surgery [10]. When VTE chemoprophylaxis

FDA device/drug status: Not applicable.

Author disclosures: ***RR:*** Nothing to disclose. ***SE:*** Nothing to disclose. ***SS:*** Nothing to disclose. ***GS:*** Nothing to disclose. ***TA:*** Nothing to disclose.

* Corresponding author. Mercy Health St. Vincent Medical Center, Department of Orthopedics, 2409 Cherry St, Suite #10, Toledo, OH 43608, USA. Tel.: (419) 251-6553, fax: (419) 251-9672.

E-mail address: eaddy.sam@gmail.com (S. Eaddy).

https://doi.org/10.1016/j.xnsj.2023.100295
Received 24 August 2023; Received in revised form 16 November 2023; Accepted 17 November 2023
Available online 23 November 2023

is used, the optimal timing of administration to maximize the benefits of anticoagulation whereas minimizing bleeding risks remains unclear [11,12].

Guidelines regarding the use of chemoprophylaxis in spine surgery have generally discouraged their use [6,11]. In 2009, the North American Spine Society found insufficient evidence in the literature at that time to recommend the routine use of chemoprophylaxis in patients undergoing elective spine surgery [11]. Similarly, in 2012, the American College of Chest Physicians recommend mechanical prophylaxis over chemoprophylaxis, or no prophylaxis, with the addition of chemoprophylaxis only for high-risk patients (eg, those undergoing combined anterior and posterior approach, or in the case of paralysis, multiple trauma, malignancy, spinal cord injury, or hypercoagulable states) [6].

Although multiple studies have investigated the benefits of chemoprophylaxis in spine surgery, the results have been contradictory. Some have reported no difference in VTE incidence among those who did and did not receive chemoprophylaxis [13,14], although others have found that chemoprophylaxis was associated with a lower incidence of VTE [15,16]. Even in the case of systematic reviews and meta-analyses, the findings have been inconclusive and conflicting. A recent review by Ellenbogen et al. [7] looked at 7 spine studies and found a significant decrease in postoperative DVT with chemoprophylaxis versus no chemoprophylaxis (RR 0.42, 95% CI 0.21–0.86). In contrast, Mosenthal et al. [1] conducted a meta-analysis of 28 spine surgery studies and found no significant differences in rates of VTE in patients receiving no prophylaxis, including mechanical prophylaxis, and/or chemoprophylaxis. Most reviews conducted to date are weakened by the inclusion of all types of spine surgery. For example, studies that include patients with known individual risk factors for DVT and PE [17,18], such as trauma, cancer, or spinal injuries, add confounding populations to the overall review and limit the generalizability of any conclusions they are able to draw [12].

Venous thromboembolism chemoprophylaxis in elective spine surgery continues to be an active area of research and multiple high-quality studies have been published in this population over the last few years. Given the availability of additional studies, the inconclusive findings of previous analyses, and the continued controversy around the optimum method and timing of VTE prophylaxis during elective spinal surgery, additional analysis is warranted. The purpose of this review is to determine the overall incidence rates of VTE and SEH following elective spine surgery, and to assess how these rates are affected by the use of chemical thromboprophylaxis. This review has the potential to educate clinicians and influence the development of clinical guidelines on the use of pharmacologic anticoagulation in elective spine surgery.

Methods

Study design

A systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [19]. Before performing the literature search, a study protocol was established and disclosed in the International Prospective Register of Systematic Reviews database in May of 2022 (ID: CRD42022321575).

Search strategy

Literature searches were performed in 3 databases including PubMed, EMBASE, and Cochrane through July 2023. The research was focused on studies comparing the use of chemical prophylaxis and no chemical prophylaxis in patients undergoing elective spine surgery. Boolean operators were used to combine a variety of key terms such as “prophylaxis,” “spine-surgery,” “venous-thromboembolism,” and “spinal-epidural-hematoma”. The search strategy used for each database is provided in Supplementary Table 1.

Study screening

A comprehensive database search identified a total of 782 studies. Titles and abstracts were screened by 2 independent reviewers and duplicate studies were removed. Full articles were then assessed to confirm eligibility and any disagreements were resolved by a third reviewer. The bibliographies of relevant articles were routinely reviewed for potentially eligible studies. Of the 735 articles screened for eligibility, 19 studies were included in this review.

Inclusion and exclusion criteria

Studies published between January 2000 and July 2023 that compared clot-related complications in patients undergoing elective spinal surgery were assessed for eligibility. Studies were excluded for the following reasons: (1) patients under 18 years old, (2) insufficient details on surgery or outcomes, (3) spine trauma surgery, (4) opinions/editorials/letters, abstracts/conference posters, technical reports, systematic reviews/meta-analyses, nonclinical papers (in vitro, in vivo, animal, in silico), (5) case report/series with <5 patients, (6) English translation unavailable, and (7) unrelated studies.

Risk of bias

The Newcastle-Ottawa Scale (NOS) was used to assess risk of bias of the nonrandomized cohort and case-control studies that were included in the meta-analysis [20]. The Cochrane risk of bias tool 2.0 was used to assess risk of bias for randomized controlled trials (RCT) [21]. Risk of bias for each study was independently assessed by 2 reviewers. Final decisions and disagreements were adjudicated by a third reviewer.

Data collection

Baseline patient information was extracted by 2 reviewers including age, sex, and body-mass index (BMI). Information on VTE prophylaxis included type of chemical anticoagulant, dose, the number and timing of doses, and the use of concomitant mechanical prophylaxis. Operative information was collected on the operative spinal region, procedure type, surgical approach, number of levels operated, mean operative time, and mean blood loss. The primary outcomes of interest were the incidences of VTE (including DVT and PE) and SEH.

Statistical analysis

A meta-analysis of the primary outcomes (VTE and SEH) was performed to compare cohorts that received chemical prophylaxis with those that did not. Studies were excluded from the meta-analysis if they had insufficient outcome data, disproportional outcome data (case-control studies), or if they did not directly compare a chemoprophylaxis group to a control group that did not receive chemoprophylaxis. A total of 16 studies were included in the analysis of VTE incidence and 13 studies were included in the analysis of SEH incidence. The Mantel-Haenszel odds ratio (OR) estimates were used for dichotomous variables. Heterogeneity was reported using the I^2 statistic. A random effects model was used when the I^2 statistic was over 50%, otherwise a fixed-effect model was used. Odds ratios were calculated with 95% confidence intervals to incorporate a measure of effect size. Meta-analysis was performed using Review Manager (RevMan, Version 5.4.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Study selection

A total of 782 articles were identified from the comprehensive database search and an additional 15 were identified from bibliogra-

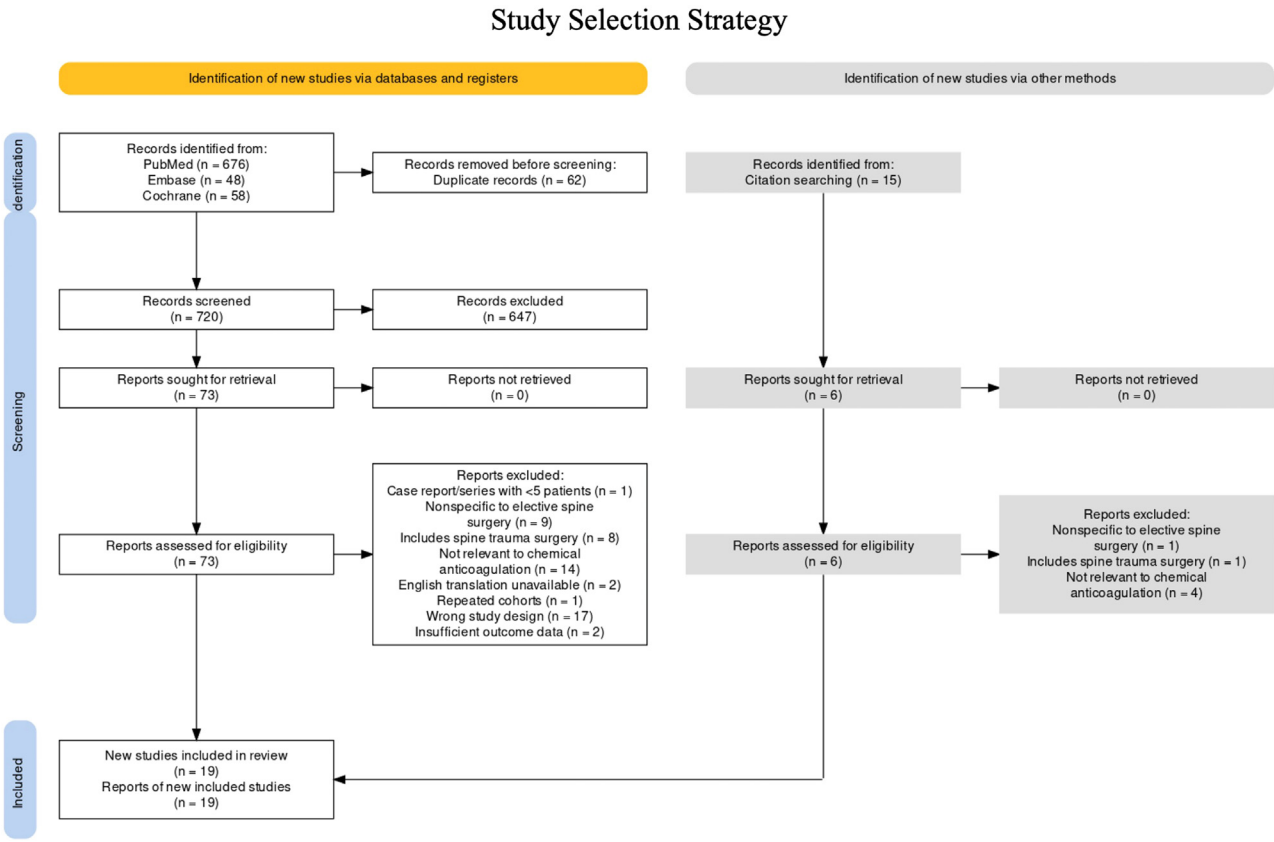

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram depicting the study selection strategy.

phies of relevant studies. After eligibility criteria were confirmed, a total of 19 studies were included in our review. The preferred reporting items for systematic reviews and meta-analyses guidelines flow diagram detailing the study selection process is illustrates in Fig. 1 [22].

Study characteristics

Baseline characteristics of the included studies are illustrated in Table 1**.** Publication dates ranged from October 2009 to February 2023. There were 11 retrospective cohort studies, 1 case series, 1 retrospective case-control study, 1 prospective cohort study, and 5 RCTs. Countries of origin included the United States (52.6%), China (15.8%), United Kingdom (10.5%), Iran (10.5%), Canada (5.3%), and Australia (5.3%). Fourteen studies used patient data from single-center institutional populations, with an average sample size of 1,145 [14,23–27,28–31,32–34,35]. Two studies used data from national databases, comprising an average sample size of 101,864 [36,37]. Collectively, a total of 220,932 patients who underwent elective spinal surgeries were included. Of these, 18.2% (40,306) were managed with chemoprophylactic anticoagulation and 81.8% (180,626) received no chemoprophylactic anticoagulation.

A variety of chemical anticoagulant medications and dosing regimens were studied. Types of chemoprophylactic agents included aspirin, heparin, low molecular weight heparin (LMWH), factor Xa inhibitors, direct thrombin inhibitors, and warfarin. The most common chemoprophylaxis agent used was LMWH, with 5 (26.3%) studies exclusively comparing the use of LMWH against no chemoprophylaxis. Two RCTs looked at the administration of intraoperative tranexamic acid with and without the use of postoperative Rivaroxaban [32,38]. Timing of chemoprophylaxis initiation was reported in all but 2 studies [14,31] and ranged from within 12 hours preoperatively to within 5 days postoperatively [26,37]. The most common period to begin anticoagulation was postoperative day 1, with 4 (23.5%) studies [23,25,33,34] initiating chemoprophylaxis strictly on postoperative day 1. The timing of initiation for each individual group is listed in Table 1.

Baseline patient characteristics

Mean patient age ranged from 47 to 66 years [28,31] among the 7 studies that reported average age for the entire sample [14,25,27–31]. Most patients were women in 8 of the 13 studies that reported sex [25,27,28,30,33,34,38,39]. The average BMI was 29.3, although sample-wide BMI averages were only reported in 5 (26.3%) studies [14,27,29,31,34]. A full list of study-level patient characteristics is provided in Table 2. Indications for spine surgery varied from degenerative disc disease to spinal canal stenosis and disc herniation. The most common spinal region being operated on was lumbar, with 7 (37%) studies exclusively studying elective lumbar procedures. Most studies excluded patients with known risk factors for thrombosis, however, exclusion criteria were not consistent across studies.

Outcomes

Venous thromboembolism

The overall pooled incidence of VTE, regardless of whether prophylaxis was used, was 3.2%. We identified one outlier with a high overall incidence of 32.5%, and this study was removed from pooled incidence calculations [40]. The incidence of VTE among patients that received chemoprophylaxis (including all chemoprophylaxis types) was 2.9%, compared with 3.6% in patients that did not receive any chemoprophylaxis. On the basis of the meta-analysis, there was no significant difference in the incidence of VTE (Fig. 2) between patients that received chemical prophylaxis and those that did not (OR 0.97, p=.95, 95% CI 0.43–2.19). Incidence rates of VTE for each study arm are illustrated in Table 3.

Table 1
Study characteristics.

Study	Study design	Group (chemoprophylaxis type)	Sample size (n)	Dose	Timing of initial dose	Mechanical prophylaxis
Nicol et al. [23]	R	1. Aspirin (or LMWH in high-risk patients)	414	150 mg	POD 1	TED
		2. None	697	-	-	Variable
Cunningham et al. [24]	RCT	1. Heparin	1,428	5,000 U	Preoperative	-
		2. None	2,442	-	-	-
Yang et al. [25]	R	1. LMWH	721	4,100 U	POD 1	Yes (unspecified)
		2. None	140	-	-	Yes (unspecified)
Hamidi et al. [26]	RCT	1. LMWH	49	40 mg	Within 12 h preoperatively	TED
		2. None	40	-	-	TED
Weber et al. [27]	CS	1. LMWH	40	-	4–6 h postoperatively	TED and SCD
		2. None	68	-	-	TED and SCD
Fawi et al. [28]	R	1. LMWH	689	40 mg	6 h postoperatively	TED
		2. None	1,677	-	-	TED
McLynn et al. [14]	R	1. Chemoprophylaxis*	1,602	-	-	SCD
		2. None	1,253	-	-	SCD
Zhang et al. [38]	RCT	1. TXA	151	TXA:1 g	Intraoperative	SCD
		2. Rivaroxaban	141	Rivaroxaban:10 mg	Postoperative	SCD
		3. TXA+Rivaroxaban	169	TXA: 1 g; Rivaroxaban: 10 mg	TXA:intraoperative; Rivaroxaban: postoperative	SCD
		4. Placebo (0.9%NaCl)	138	100 mL	Intraoperative	SCD
Shapiro et al. [29]	P	1. LMWH (Enoxaparin)	55	40 mg	24–36 h postoperatively	SCD and TED
		2. None	211	-	-	SCD
Fourman et al. [39]	R	1. Aspirin	102	Aspirin: 325 mg	POD 2	SCD
		2. Aspirin+Fondaparinux	275	Aspirin: 325 mg; Fondaparinux: 2.5 mg	POD 2	SCD
Zervos et al. [40]	CC	1. Heparin	165	5,000 U	Postoperative	-
		2. None	35	-	-	-
Kiguchi et al. [30]	R	1. Heparin ≤24 h	105	5,000 U	≤24 h postoperatively	SCD (88.6%)
		2. Heparin >24 h	70	5,000 U	>24 h postoperatively	SCD (78.6%)
		3. None	241	-	-	SCD (75.5%)
Thota et al. [31]	R	1. Chemoprophylaxis (unspecified)	888	-	-	-
		2. None	888	-	-	-
Li et al. [32]	RCT	1. TXA	212	2 g	TXA: intraoperative	Yes (unspecified)
		2. TXA+Rivaroxaban	218	TXA: 2 g; Rivaroxaban: 10 mg	TXA: intraoperative; Rivaroxaban: postoperative	Yes (unspecified)
		3. Placebo (0.9%NaCl)	227	-	15 min before skin incision	Yes (unspecified)
Fiasconaro et al. [36]	R	1. Aspirin	1,872	-	POD 0	-
		2. Heparin	26,758	-	POD 0	-
		3. LMWH	888	-	POD 0	-
		4. Warfarin	137	-	POD 0	-
		5. Multiple anticoagulants	942	-	POD 0	-
		6. None	53,242	-	POD 0	-
Pirkle et al. [37]	R	1. Chemoprophylaxis (all types)	1,168	-	Within 5 d postoperatively	-
		2. None	118,720	-	-	-
Macki et al. [33]	R	1. LMWH	281	40 mg/kg	POD 1	SCD
		2. Unfractionated heparin	281	5,000 U	POD 1	SCD
Nikouei et al. [34]	RCT	1. Aspirin	41	325 mg	POD 1	-
		2. None	41	-	-	Yes (unspecified)
Cloney et al. [35]	R	1. Chemoprophylaxis (unfractionated heparin or LMWH or fondaparinux)	444	Unfractionated heparin: 5000 U; enoxaparin: 40mg; dalteparin: 2,500 U or 5,000 U; fondaparinux: 2.5 mg	POD 1–3	SCD
		2. None	566		-	SCD

-, not reported; R, retrospective cohort; RCT, randomized controlled trial; CS, case series; P, prospective cohort; CC, case-control; LMWH, low molecular weight heparin; TXA, tranexamic acid; POD, postoperative day; SCD, sequential compression device; TED, thromboembolic deterrent stockings; BMI, body-mass index; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; SEH, spinal epidural hematoma.

* Unfractionated heparin (97.1%), LMWH (2.5%), warfarin (0.3%).

Deep vein thrombosis and pulmonary embolism

Among studies that reported DVT and PE outcomes independently, the overall pooled incidence rates were 3.3% and 0.4%, respectively. Patients managed with chemoprophylaxis had a DVT incidence of 2.7%, whereas those who were not had an incidence of 3.9%. The incidence of PE in the chemoprophylaxis group was 0.2% compared with 0.3% in controls.

Spinal epidural hematomas

Of the 16 studies that reported SEH as an outcome, the overall incidence was 0.4%. This rate did not change regardless of whether patients received chemoprophylaxis or not. Based on the meta-analysis, there was no significant difference in the incidence of SEH (Fig. 3) between the two groups (OR 1.57, p=.06, 95% CI 0.99–2.50). Study-specific incidence rates for SEH are illustrated in Table 3.

Table 2
Study-specific patient characteristics.

Study	Group (chemoprophylaxis type)	Age (y)	Women	BMI (kg/m^2)	Operative spinal region (n)
Nicol et al. [23]	1. Aspirin	-	-	-	All lumbar
	2. None	-	-	-	
Cunningham et al. [24]	1. Heparin	-	-	-	Cervical, thoracic, thoracolumbar
	2. None	-	-	-	
Yang et al. [25]	1. LMWH	-	-	-	Cervical, thoracic, lumbar
	2. None	-	-	-	
Hamidi et al. [26]	1. LMWH	53.4±15.7	21 (42.9)	27.2±4.0	Cervical (8), thoracic (1), lumbar (29), multi (2)
	2. None	50.1±13.8	22 (55.0)	27.1±4.1	Cervical (12), thoracic (1), lumbar (35), multi (1)
Weber et al. [27]	1. LMWH	58±12.0	56 (52.3)	29.8±6.1	All lumbar
	2. None	-	-	-	
Fawi et al. [28]	1. LMWH	46.8	353 (51.2)	-	Thoracic, thoracolumbar, lumbar
	2. None	-	944 (56.3)	-	
McLynn et al. [14]	1. Chemoprophylaxis	56.0±14.7	1364 (47.8)	29.5±5.7	Cervical, thoracic, lumbar
	2. None	-	-	-	
Zhang et al. [38]	1. TXA	54.7±9.9	94 (62.3)	25.8±3.3	All lumbar
	2. Rivaroxaban	59.2±10.2	85 (60.3)	25.9±3.5	
	3.TXA+Rivaroxaban	58.3±10.5	117 (69.2)	25.4±3.3	
	4. Placebo	57.0±10.2	91 (66.0)	25.2±3.5	
Shapiro et al. [29]	1. LMWH	56.8±13.7	-	30.3±6.3	Cervical, thoracolumbar
	2. None	-	-	-	
Fourman et al. [39]	1. Aspirin	59.0±14.5	-	30.8±7.7	Thoracolumbar, lumbar, lumbosacral
	2.Aspirin+Fondaparinux	61.7±13.0	-	31.3±6.7	
Zervos et al. [40]	1. Heparin	61.1±12.3	-	30.7±5.7	Cervical (23), lumbar (42)
	2. None	65.5±12.1	-	31.6±7.1	Cervical (48), lumbar (87)
Kiguchi et al. [30]	1. Heparin ≤24 h	57.8±12.5	69 (65.7)	-	All lumbar
	2. Heparin >24 hours	61.2±11.2	50 (71.4)	-	
	3. None	61.3±12.8	150 (62.2)	-	
Thota et al. [31]	1. Chemoprophylaxis	66.6±12.1	411 (46.3)	29.8±6.0	-
	2. None	65.7±13.2	411 (46.3)	29.5± 6.1	-
Li et al. [32]	1. TXA	55.5±10.6	138 (65.1)	25.7±3.3	All lumbar
	2.TXA+Rivaroxaban	56.8±10.5	140 (64.2)	25.8±3.3	
	3. Placebo	55.3±10.4	143 (63.0)	25.7±3.6	
Fiasconaro et al. [36]	1. Aspirin	-	-	-	Cervical, lumbar
	2. Heparin	-	-	-	
	3. LMWH	-	-	-	
	4. Warfarin	-	-	-	
	5. Multiple anticoagulants	-	-	-	
	6. None	-	-	-	
Pirkle et al. [37]	1. Chemoprophylaxis	-	-	-	Cervical, lumbar
	2. None	-	-	-	
Macki et al. [33]	1. LMWH	60.9±12.2	144 (51.2)	-	Cervical, cervicothoracic, thoracic, thoracolumbar, lumbar
	2. Unfractionated heparin	60.8±12.3	166 (59.1)	-	
Nikouei et al. [34]	1. Aspirin	63.2±7.1	25 (61.0)	26.5±4.1	All lumbar
	2. None	64.3±6.6	27 (65.9)	27.6±5.9	
Cloney et al. [35]	1. Chemoprophylaxis	-	181 (54.7)	-	All lumbar
	2. None	-	146 (59.9)	-	

-, not reported; LMWH, low molecular weight heparin; TXA, tranexamic acid; POD, postoperative day; BMI, body-mass index.
Data presented as n (%) or mean±standard deviation unless otherwise stated.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was performed for the 12 non-randomized cohort and case-control studies that were included in the meta-analyses (Table 4) [20]. The mean NOS score was 7.6±1.3. Ten of 12 studies were classified as good quality, one was fair quality, and one was poor quality. Each of the 4 randomized controlled studies were assessed by the Cochrane Risk of Bias 2.0 Tool (Fig. 4) [21]. All four were found to have an overall low risk of bias, despite 2 studies raising some concern for the randomization process. Both studies randomized patients based on the stratification of their risk factors to ensure that only patients deemed to have a high-risk of thrombosis were selected for the groups receiving chemical anticoagulation [32,38].

Discussion

Venous thromboembolism is a common postoperative complication that can raise the risks of morbidity and mortality [7,11]. Because of this, prevention of VTE has been heavily studied among other orthopedic and trauma surgery populations [12]. For instance, there is robust evidence to suggest that prophylactic anticoagulation significantly reduces the occurrence of VTE after hip and knee arthroplasty [41]. The efficacy of prophylactic anticoagulation in spine surgery, however, is not well defined. Despite clinical guidelines set forth by the National Academy of Spine Surgeons in 2009, there is still no consensus about perioperative VTE prophylaxis among the spine community [12,42]. To address this lack of consensus, AO Spine conducted a global survey to gauge current attitudes and practices of spine surgeons towards prophylactic anticoagulation. Among 316 respondents, 70.3% routinely used risk-stratification techniques when deciding whether to use anticoagulation, but only 14.4% cited clinical guidelines as their main source for stratification. However, 91.8% of surgeons reported that they would adopt anticoagulation guidelines if they were to be established [42]. Although the majority of research on this topic has focused on hospitalized patients, numerous studies in recent years have looked specifically at elective surgery populations. Therefore, the purpose of this review was to summarize the incidence rates of VTE and SEH in the context of prophylactic anticoagulation use in elective spine surgery.

We analyzed a total of 19 studies (220,932 patients) and found the overall rate of VTE to be 3.2% after a single outlier was removed. Patients that received some form of chemical anticoagulation were only slightly less likely to experience a VTE event (OR 0.97) compared with those that did not, and this result was not significant (p=.95, 95% CI 0.43–2.19). The overall incidence rate of SEH was low at 0.4%, which

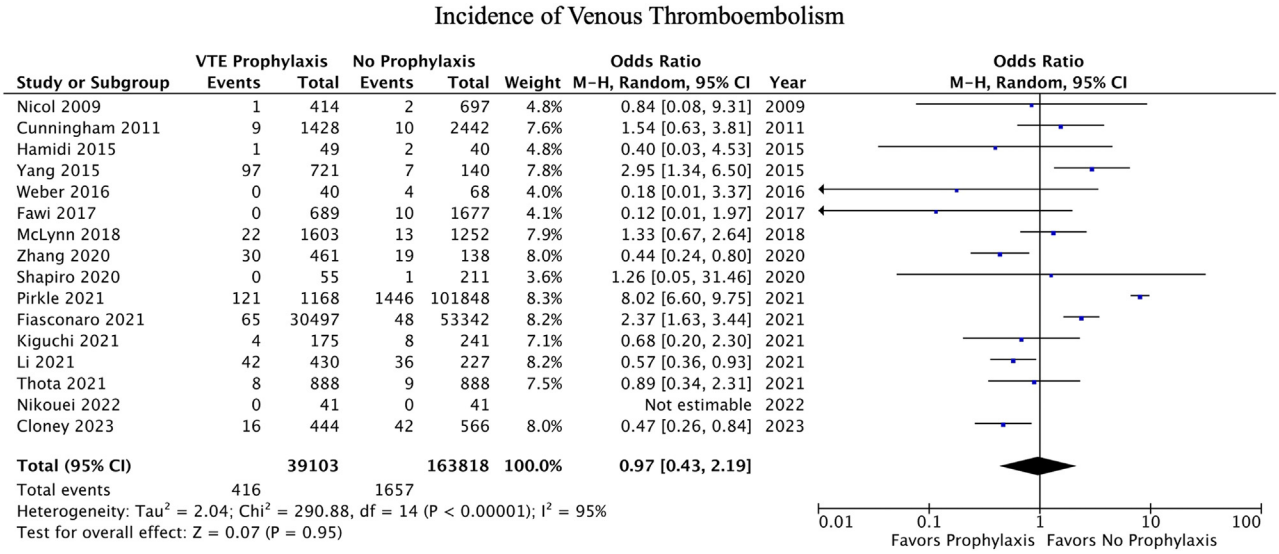

Fig. 2. Forest plot depicting meta-analysis results for the comparison of VTE incidence between patients that did and did not receive perioperative VTE chemoprophylaxis. VTE, venous thromboembolism.

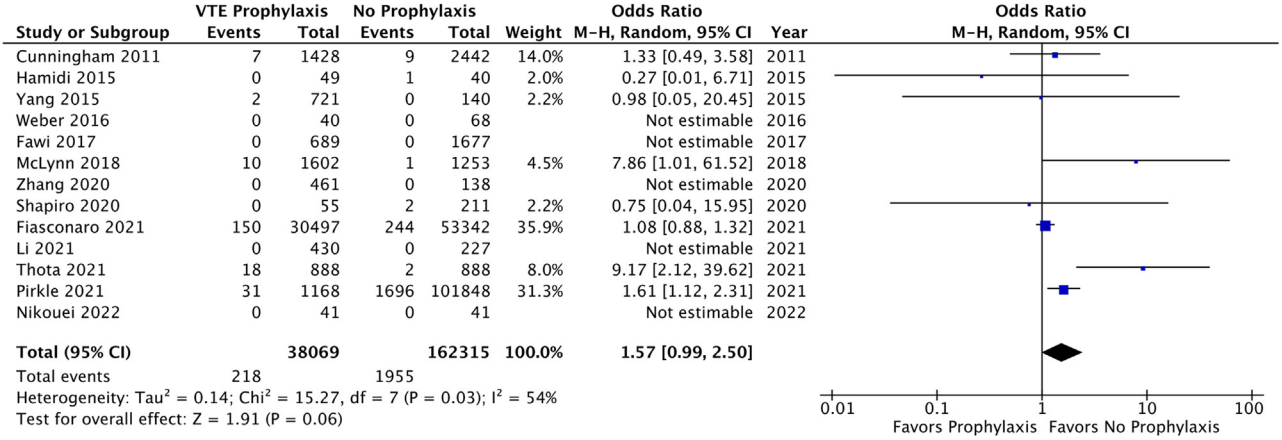

Fig. 3. Forest plot depicting meta-analysis results for the comparison of SEH incidence between patients that did and did not receive perioperative VTE chemoprophylaxis. VTE, venous thromboembolism; SEH, spinal epidural hematomas.

is consistent across other reviews. The use of anticoagulant medications did not increase the incidence of SEH in this population. In fact, the odds of SEH were higher among patients that did not receive chemoprophylaxis (OR 1.57), although this was marginally insignificant (p=.06, 95% CI 0.99–2.50).

Some of the included studies had substantially higher incidence rates of VTE than others. Studies that used routine postoperative screening for thrombosis with ultrasonography, regardless of symptomatic events, consistently reported higher rates of VTE for both groups [25,32,38]. Two RCTs assigned patients to groups based on a scored preoperative risk of thrombosis, whereby patients at high risk of thrombosis (as determined by an Autar score >10) received chemoprophylaxis postoperatively. Nonetheless, the rates of VTE among these chemoprophylaxis groups (9.8% and 6.5%) were higher than rates seen in most other studies [32,38]. Zervos et al. [40] was identified as an outlier caused by an unusually high overall incidence rate of 32.5%. This was a case-control study that selectively reviewed 65 cases of postoperative DVT compared with 135 matched controls without DVT, which led to a skewed calculation of incidence in the context of this review.

Other systematic reviews have assessed the elective surgery population with varying results. After analyzing 14 studies, Sansone et al. [5] also found that the use of chemoprophylaxis significantly reduced the prevalence of DVT relative to either mechanical prophylaxis (p=.047) or no prophylaxis (p<.01). Our results are supported by Schuster et al. [43], who performed a systematic review of elective thoracolumbar surgeries and found that the use of chemoprophylaxis did not change the risk of VTE, although only 2 studies were included in their review [44]. The most recent systematic review involving elective spine surgery was published by Colomina et al. [12] in 2020 and included 6 studies, however the authors were unable to reach a clear conclusion about the advantages and disadvantages of chemoprophylaxis. Of note, this review excluded studies that contained groups of patients that did not receive chemoprophylaxis. Because of that, an additional 3 RCT and 4 retrospective cohort studies investigating the role of prophylactic anticoagulation in elective spine surgery have been published. This highlights the growing relevance of this topic and further supports the need for an updated review.

Unlike Mosenthal et al. [1], our review did not stratify analyses based on the use of mechanical prophylaxis. Instead, we compared patients that did or did not receive chemoprophylaxis, regardless of whether mechanical prophylaxis was used. Postoperative mechanical prophylaxis has become a standard of care for most operative procedures, which is

Table 3
Study-specific incidence rates of VTE and SEH.

Study	Group (chemoprophylaxis type)	VTE (both DVT+PE)	DVT	PE	SEH
Nicol et al. [23]	1. Aspirin	1 (0.2)	1 (0.2)	0 (0)	-
	2. None	2 (0.3)	2 (0.3)	0 (0)	-
Cunningham et al. [24]	1. Heparin	9 (0.6)	-	-	7 (0.5)
	2. None	10 (0.4)	-	-	9 (0.4)
Yang et al. [25]	1. LMWH	97 (13.5)	97 (13.5)	0 (0)	2 (0.3)
	2. None	7 (5)	7 (5)	0 (0)	0 (0)
Hamidi et al. [26]	1. LMWH	1 (2)	0 (0)	1 (2)	0 (0)
	2. None	2 (5)	2 (5)	0 (0)	1 (2.5)
Weber et al. [27]	1. LMWH	0 (0)	0 (0)	0 (0)	0 (0)
	2. None	4 (5.9)	2 (2.9)	2 (2.9)	0 (0)
Fawi et al. [28]	1. LMWH	0 (0)	0 (0)	0 (0)	0 (0)
	2. None	10 (0.6)	1 (0.1)	9 (0.5)	0 (0)
McLynn et al. [14]	1. Chemoprophylaxis	22 (1.4)	-	-	10 (0.6)
	2. None	13 (1)	-	-	1 (0.1)
Zhang et al. [38]	1. TXA	20 (13.2)	20 (13.2)	0 (0)	0 (0)
	2. Rivaroxaban	3 (2.1)	3 (2.1)	0 (0)	0 (0)
	3. TXA+Rivaroxaban	7 (4.1)	7 (4.1)	0 (0)	0 (0)
	4. Placebo	19 (13.8)	19 (13.8)	0 (0)	0 (0)
Shapiro et al. [29]	1. LMWH	0 (0)	0 (0)	0 (0)	0 (0)
	2. None	1 (0.5)	1 (0.5)	0 (0)	2 (0.9)
Fourman et al. [39]	1. Aspirin	5 (4.9)	3 (2.9)	2 (2.0)	0 (0)
	2.Aspirin+Fondaparinux	1 (0.4)	0 (0)	1 (0.4)	0 (0)
Zervos et al. [40]	1. Heparin	57 (34.5)	57 (34.5)	-	1 (0.6)
	2. None	8 (22.9)	8 (22.9)	-	0 (0)
Kiguchi et al. [30]	1. Heparin ≤24 h	2 (1.9)	-	-	-
	2. Heparin >24 h	2 (2.9)	-	-	-
	3. None	8 (3.3)	-	-	-
Thota et al. [31]	1. Chemoprophylaxis	8 (0.9)	-	3 (0.3)	18 (2.0)
	2. None	9 (1)	-	3 (0.3)	2 (0.2)
Li et al. [32]	1. TXA	34 (16.0)	34 (16)	0 (0)	0 (0)
	2. TXA + Rivaroxaban	8 (3.7)	8 (3.7)	0 (0)	0 (0)
	3. Placebo	36 (15.9)	36 (15.9)	0 (0)	0 (0)
Fiasconaro et al. [36]	1. Aspirin	4 (0.2)	-	-	5 (0.3)
	2. Heparin	54 (0.2)	-	-	134 (0.5)
	3. LMWH	0 (0)	-	-	8 (0.9)
	4. Warfarin	1 (0.7)	-	-	1 (0.7)
	5. Multiple anticoagulants	6 (0.6)	-	-	2 (0.2)
	6. None	48 (0.1)	-	-	244 (0.5)
Pirkle et al. [37]	1. Chemoprophylaxis	121 (10.4)	-	-	31 (2.7)
	2. None	2,907 (2.4)	-	-	2332 (2.0)
Macki et al. [33]	1. LMWH	4 (1.4)	4 (1.4)	-	1 (0.4)
	2. Unfractionated heparin	4 (1.4)	4 (1.4)	-	4 (1.4)
Nikouei et al. [34]	1. Aspirin	0 (0)	0 (0)	-	0 (0)
	2. None	0 (0)	0 (0)	-	0 (0)
Cloney et al. [35]	1. Chemoprophylaxis	16 (3.6)	-	-	-
	2. None	42 (7.4)	-	-	-

-, not reported; LMWH, low molecular weight heparin; TXA, tranexamic acid; POD, postoperative day; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; SEH, spinal epidural hematoma.
Data presented as n (%).

why we choose to focus on the implications of chemical prophylaxis. However, we recognize there is potential for combined anticoagulatory effects and thus skewed results among patients that received both forms of prophylaxis. The design of our meta-analysis was also limited to the comparison of VTE incidence as a whole and did not include relative sub-analyses of DVT and PE. In a meta-analysis conducted by Ellenbogen et al. [7] of 7 general spine surgery studies, the incidence of DVT was significantly lower in patients receiving chemoprophylaxis compared with those that did not, despite no significant difference in the overall rate of VTE.

The main limitation in this review is the heterogeneity among the included studies. There was significant variation across numerous influential factors including baseline patient characteristics and comorbidities, spinal procedures and approaches performed, types of chemical anticoagulation, timing and duration of chemoprophylaxis, and methods of diagnosis, among others. Variation in surgery type is particularly important to consider, as rates of VTE and postoperative bleeding can vary for different procedures and thus may alter the risks and benefits associated with prophylactic anticoagulation. The statistical heterogeneity (I^2) for the meta-analysis of VTE and SEH incidence was 95% and 54%, respectively, thus, a random effects model was used. This review is also limited by the quality of the available studies. Few RCTs have been conducted on this topic in the elective spine surgery population. Although we determined the overall risk of bias to be low among each of the four RCTs, 2 studies raised some concern for the quality of their randomization process [32,38]. Quality assessment of the included observational studies identified one study as “fair” quality caused by deficits in cohort selection, and another as “poor” with deficits in each of the selection, comparability, and outcome domains [25,29]. In many studies, key variables and relevant information were not well-defined, which further contributed to the inconsistency. Given the significant heterogeneity and quality concerns within several studies, we acknowledge that our findings should be taken with caution. The overall pooled incidence rates in this review, as well as the nonsignificant effects of chemoprophylaxis on the rates of VTE and SEH, are by no means definitive for the entire elective spine surgery population.

To the best of our knowledge, this is the largest systematic review and meta-analysis of thrombotic chemoprophylaxis in the elective spine surgery population. We believe a strength of this review is that it captures a recent rise in publications on this topic, however, additional RCTs are needed. We recommend that future studies focus on delineating the effects of chemoprophylaxis on various subpopulations of

Table 4
Newcastle-ottawa scale results for nonrandomized studies included in the meta-analysis.

Study	Criteria*								Quality result†
	Selection				Comparability	Exposure			
	1	2	3	4	5	6	7	8	
Nicol et al. [23]	1	1	1	1	1	1	1	1	Good
Cunningham et al. [24]	1	1	1	1	2	1	1	1	Good
Yang et al. [26]	1	0	1	1	0	1	0	1	Poor
Weber et al. [27]	1	0	1	1	1	1	1	1	Good
Fawi et al. [29]	1	1	1	1	2	1	1	1	Good
McLynn et al. [14]	1	1	1	1	2	1	1	1	Good
Shapiro et al. [31]	1	0	1	0	1	1	1	1	Fair
Kiguchi et al. [30]	1	1	1	1	1	1	1	1	Good
Thota et al. [35]	1	1	1	1	1	1	1	1	Good
Fiasconaro et al. [37]	1	0	1	1	1	1	0	1	Good
Pirkle et al. [37]	1	1	1	1	2	1	1	1	Good
Cloney et al. [35]	1	1	1	0	1	1	1	1	Good

* 1, representativeness of the exposed cohort; 2, selection of the nonexposed cohort; 3, ascertainment of exposure; 4, demonstration that outcome of interest was not present at start of the study; 5, comparability of cohorts on the basis of the design or analysis; 6, assessment of the outcome (independent assessment or record linkage); 7, was follow-up long enough for outcomes to occur? (minimum of 30 days); 8, adequacy of follow-up (lost to follow-up rate >10% is inadequate).

† Good: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Fair: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; Poor: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

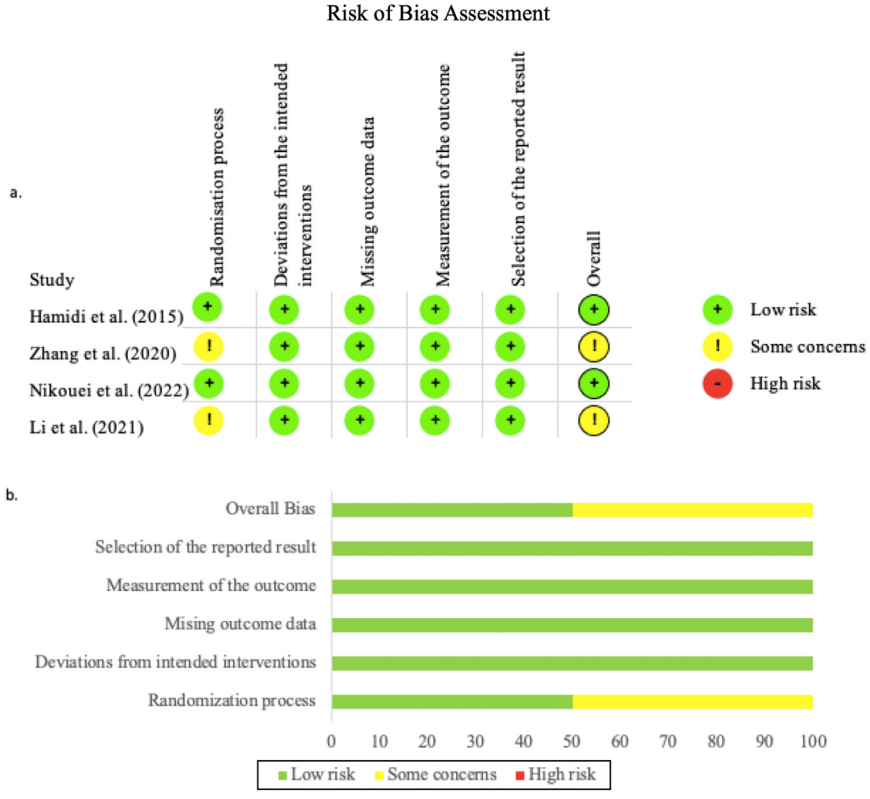

Fig. 4. Risk of bias assessment for randomized studies included in the meta-analysis using the Cochrane Risk of Bias Tool 2.0. (A) Traffic light plot depicting the authors' judgments of individual bias domains for each study. (B) Graph demonstrating authors' judgments of each bias domain across all included studies as percentages and relative risks. VTE, venous thromboembolism.

elective spine surgery procedures, while controlling for different types, timing, and duration of prophylaxis.

Conclusions

Venous thromboembolism remains a common and potentially devastating postoperative complication for patients undergoing spine surgery. Among the 19 studies that met eligibility criteria, we found the pooled incidence of VTE to be 3.2% overall, 2.9% in patients receiving chemoprophylaxis, and 3.6% in patients that did not receive chemoprophylaxis. Despite a reduced incidence of VTE in patients receiving chemoprophylaxis, this was not a statistically significant difference. Our findings also suggest that the use of chemoprophylaxis may not make a significant difference in the rates of spinal epidural hematomas following elective spine surgery. We identified a substantial degree of heterogeneity among the available literature; thus, our findings should be taken with caution. In spite of this, this review summarizes the current landscape of literature on thromboprophylaxis in elective spine surgery for clinicians and patients and has the potential to shape the future development of refined clinical guidelines. Future studies should better define the efficacy of specific prophylactic protocols in subpopulations of elective spine surgery that are most at risk of thrombotic complications.

Declarations of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All data relevant to the study are included in the manuscript and its tables.

Acknowledgments

The authors thank Alexander Mebane, Annie Steffensen, and John Pederson, who provided assistance with study design, protocol development, and database searches on behalf of superior medical experts.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2023.100295.

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