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THE USE OF CHEMOPROPHYLAXIS OR NOT FOR DVT IN SPINE SURGERY: A SYSTEMATIC REVIEW

O USO DA QUIMIOPROFILAXIA OU NÃO PARA TVP EM CIRURGIA DE COLUNA: REVISÃO SISTEMÁTICA

EL USO DE QUIMIOPROFILAXIS O NO PARA LA TVP EN LA CIRUGÍA DE COLUMNA VERTEBRAL: REVISIÓN SISTEMÁTICA

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ABSTRACT

Objective: To compare pharmacological and non-pharmacological prophylaxis in elective spine surgery to determine the risks of DVT, PTE, and epidural hematoma (EH) in both groups, as well as their respective treatment effectiveness. Methods: Systematic review and meta-analysis based on systematically searched articles, using combinations of MeSH terms related to chemoprophylaxis and non-chemoprophylaxis for prevention of deep vein thrombosis and pulmonary embolism in elective spine surgery. Adult patients were eligible for inclusion in the study, except for those with trauma, spinal cord injury, neoplasms, or those using vena cava filters. Results: Five studies were selected for this systematic review and meta-analysis: 3 retrospective studies, 1 prospective study, and 1 case series. Data analysis showed that 4.64% of patients treated with chemoprophylaxis had an unfavorable outcome regarding DVT, while this outcome occurred in 1.14% of patients not treated with chemoprophylaxis (p=0.001). Among patients using chemoprophylaxis, only 0.1% developed epidural hematoma and 0.38% developed PTE. Among those on non-pharmaceutical prophylaxis, 0.04% had EH (p=0.11) and 0.42% had PTE (p=0.45). Conclusions: No benefits were found for chemoprophylaxis as compared to non-chemoprophylaxis in preventing DVT in elective spine surgery, nor was there an increased risk of epidural hematoma or fatal thromboembolic events. ***Level of evidence III; Therapeutic studies; Investigation of treatment results.***

Keywords: Chemoprevention; Venous Thrombosis; Pulmonary Embolism; Spinal Epidural Hematoma; Spine; Systematic Review.

RESUMO

Objetivo: Comparar profilaxia farmacológica e não farmacológica em cirurgia eletiva da coluna vertebral, a fim de determinar os riscos de TVP, TEP e hematoma epidural (HE) em ambos os grupos, bem como a respectiva eficácia do tratamento. Métodos: Revisão sistemática e metanálise com base em artigos sistematicamente pesquisados, usando combinações de termos MESH relacionados à quimioprofilaxia e à não quimioprofilaxia para prevenção de trombose venosa profunda e embolia pulmonar em cirurgia eletiva da coluna vertebral. Pacientes adultos foram elegíveis para inclusão no estudo, exceto aqueles com trauma, lesão medular, neoplasias e aqueles que usavam filtros de veia cava. Resultados: Cinco estudos foram incluídos para fazer parte desta revisão sistemática e metanálise: três estudos retrospectivos, um prospectivo e um série de casos. A análise dos dados mostrou que 4,64% dos pacientes tratados com quimioprofilaxia tiveram um resultado desfavorável em relação à TVP, enquanto esse resultado ocorreu em 1,14% dos pacientes não tratados com quimioprofilaxia (p = 0,001). Entre os pacientes em uso de quimioprofilaxia, apenas 0,1% desenvolveram hematoma epidural (HE) e 0,38% desenvolveram TEP. Entre aqueles em profilaxia não medicamentosa, 0,04% apresentaram HE (p = 0,11) e 0,42% tiveram TEP (p = 0,45). Conclusões: Não foram encontrados benefícios para a quimioprofilaxia quando comparada à não quimioprofilaxia na prevenção da TVP em cirurgia eletiva da coluna vertebral, assim como não foi verificado aumento do risco de hematoma epidural ou eventos tromboembólicos fatais. ***Nível de evidência III;*** **Estudos terapêuticos - Investigação dos resultados do tratamento.**

Descritores: *Quimioprevenção; Trombose Venosa; Embolia Pulmonar; Hematoma Epidural Espinal; Coluna Vertebral; Revisão Sistemática.*

RESUMEN

Objetivo: Comparar la profilaxis farmacológica y no farmacológica en la cirugía de columna electiva para determinar los riesgos de TVP, TEP y hematoma epidural (HE) en ambos grupos, así como la respectiva eficacia del tratamiento. Métodos: Revisión sistemática y metanálisis basados en artículos buscados sistemáticamente, utilizando combinaciones de términos MESH relacionados con quimioprofilaxis y no quimioprofilaxis para la prevención de trombosis venosa profunda y embolia pulmonar en cirugía electiva de columna. Se eligieron pacientes adultos para su inclusión en el estudio, excepto aquellos con traumatismos, lesión medular, neoplasias y aquellos que usan filtros de vena cava. Resultados: Se incluyeron cinco estudios para formar parte de esta revisión sistemática y metanálisis: 3 estudios retrospectivos, 1

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prospectivo y 1 serie de casos. El análisis de los datos reveló que el 4,64% de los pacientes tratados con quimioprofilaxis tuvieron un resultado desfavorable con respecto a la TVP, mientras que este resultado se produjo en el 1,14% de los pacientes no tratados con quimioprofilaxis (p = 0,001). Entre los pacientes que recibieron quimioprofilaxis, sólo el 0,1% desarrolló hematoma epidural (HE) y el 0,38% desarrolló TEP. Entre los que recibieron profilaxis no farmacológica, el 0,04% desarrolló HE (p = 0,11) y el 0,42% desarrolló TEP (p = 0,45). Conclusiones: No se encontraron beneficios para la quimioprofilaxis en comparación con la no quimioprofilaxis para prevenir la TVP en la cirugía de columna electiva, así como tampoco un mayor riesgo de hematoma epidural o eventos tromboembólicos fatales. ***Nivel de evidencia - III;*** **Estudios terapéuticos – Investigación de los resultados del tratamiento.**

Descriptores: *Quimioprevención; Trombosis Venosa; Embolia Pulmonar; Hematoma Epidural Espinal; Columna Vertebral; Revisión Sistemática.*

INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE), is a possible complication in spine surgery. The main risk factors are related to the components of Virchow's triad – stasis of blood flow, endothelial injury, and hypercoagulability,[1] which are manifested in neoplasms, advanced age, immobilization, pregnancy, coagulation disorders (hereditary or acquired), use of estrogen, and invasive procedures.[2,3] As such, most patients who undergo major surgical interventions must be assessed for risk of VTE.

In the USA, the VTE incidence is estimated at 100 per 100,000 inhabitants, with PTE accounting for 33.4% and DVT accounting for 66.6%, with mortality rates of 12% and 6% in the first month, respectively.[4] Brazilian studies focusing on pulmonary thromboembolism incidence are rare, although autopsy data demonstrate PTE prevalence rates varying between 3.9% and 16.6%.[4,5]

In orthopedic surgery, there is a considerable debate among health professionals as to the use of chemoprophylaxis to prevent venous thromboembolism. Some protocols recommend chemoprophylaxis for knee and hip replacement surgery.[6,7]

The risk of VTE is not well defined in patients undergoing spinal surgery. The data from the US reports the lowest quoted rates for lumbosacral spinal procedures as 0.6% for DVT and 0.3% for PE.[8]

Regarding spine surgery, the discussion is divided between two basic issues. On one hand, there is the need to prevent complications, which mainly involve thromboembolic phenomena, such as PTE, that can lead to death and affect some 5% to 15% of patients not treated for DVT.[9] On the other hand, chemoprophylaxis tends to result in a greater risk of postoperative epidural bleeding, which may cause neurologic symptoms and require emergency decompression. There are few clinical studies with high levels of evidence on the use of chemoprophylaxis for prevention of DVT in spine surgery.[10]

According to Dhillon et al., the risks of spinal epidural hematoma among patients who receive chemoprophylaxis and those who do not are low and equivalent. VTE complications after spine surgery typically occur within the first three postoperative days and anticoagulation therapy from one day before to three days after the surgery is safe for patients at high risk for VTE.[11] This data has led some departments to adopt a non-chemoprophylaxis strategy, with compression stockings and/or intermittent compression boots.

The objective of this study is therefore to assess and compare advantages and disadvantages of chemoprophylaxis in elective spine surgery, to determine the risks of the primary events of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) and of secondary epidural hematoma (EH) events, as well as to highlight possible clinical correlations and provide enlightenment regarding questions raised about this theme. We propose a systematic review of recent literature, using scientific article databases, with the aim of shedding more light on this theme and also to define VTE prophylaxis procedures in health services.

METHODS

Search Strategy

This study was conducted using the following guidelines: Meta-analysis of Observational Studies in Epidemiology: A Proposal for Reporting (MOOSE),[12] Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement,[13] and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[14] We performed electronic searches (prior to January 2019) in the following databases: MEDLINE/PubMed, BVS (Biblioteca Virtual da Saúde), BINACIS – AR, IBECS – ES, LILACS, and the Cochrane Central Register.

The MeSH terms (Medical Subject Headings) included in the PubMed search were: "(SPINE SURGERY) AND (((DEEP VEIN THROMBOSIS OR DEEP VENOUS THROMBOSIS OR DEEP-VEIN THROMBOSIS OR DEEP-VENOUS THROMBOSIS OR THROMBOSIS, DEEP VEIN) AND (EMBOLISM, PULMONARY OR EMBOLISMS, PULMONARY OR PULMONARY EMBOLISMS)) OR ((DEEP VEIN THROMBOSIS OR DEEP VENOUS THROMBOSIS OR DEEP-VEIN THROMBOSIS OR DEEP-VENOUS THROMBOSIS OR THROMBOSIS, DEEP VEIN)) OR ((EMBOLISM, PULMONARY OR EMBOLISMS, PULMONARY OR PULMONARY EMBOLISMS))) AND (((ANTICOAGULANT OR ANTICOAGULANT AGENTS OR ANTICOAGULANT DRUGS OR ANTICOAGULATION AGENTS AND (PROPHYLAXIS)) OR (ANTICOAGULANT OR ANTICOAGULANT AGENTS OR ANTICOAGULANT DRUGS OR ANTICOAGULATION AGENTS) OR (PROPHYLAXIS)))."

Selection criteria

This systematic review and meta-analysis included all observational study designs published in English, Spanish, Portuguese, and German which, either in articles or through retrievable data, correlate the use of chemoprophylaxis with the use of non-chemoprophylaxis in elective spine surgery to prevent thromboembolic events among adult patients (≥ 18 years old).

We have included retrospective studies, prospective studies, and case series for the analysis, and excluded studies that correlate data on surgical oncology (primary or secondary tumor), trauma, patients using vena cava filters, or with neurological damage that could not be separated, as well as articles relating to pediatric surgery or articles in languages other than those defined for our inclusion criteria.

The quality of the studies was analyzed independently by all authors and then in group discussion for consensus. Once duplicated articles were removed, two of the authors independently reviewed titles and abstracts to determine which studies met the inclusion criteria. Doubts and disagreements about selection were discussed with a third author. Following the analysis of titles and abstracts, the articles were selected by means of full-text analysis. Bibliographic references contained in the selected articles were used as sources of additional publications.

Data retrieval

The data retrieved from the final articles included: total number of patients, mean age, number of male and female patients, type of surgery performed, methods of thromboembolic event identification, number of patients using chemoprophylaxis, number of patients not using chemoprophylaxis, drugs and techniques used to prevent thromboembolic events, and number of cases with deep vein thrombosis (DVT), pulmonary thromboembolism (PTE) and epidural hematoma (EH) in the two study groups. The data were retrieved independently by two of the authors. Doubts and disagreements about epidemiological data were settled through consensus between all the authors.

The authors used Review Manager 5.3® to correlate effects, risk, and prevalence of data of interest. A random effect meta-analysis model was used to tabulate the statistics, using the Mantel-Haenszel statistical method with measurement of the relative risk effect (risk ratio), with the aim of minimizing study heterogeneity effects. Heterogeneity was calculated using Higgins' statistical inconsistency test (I^2). Coefficient correlation and a 95% confidence interval were used on a forest plot to report the intensity of individual correlation and result correlation.

RESULTS

Out of the 322 studies initially selected, 103 were removed as duplicates or for using combined data from previous studies, and another 112 articles were removed after secondary analysis. After this stage, the abstracts of the remaining 107 studies were reviewed, leading to exclusion of another 42 articles. Sixty-five articles were analyzed by means of full-text readings by all the authors. Sixty of them were then removed. The five remaining studies were accepted for inclusion in this systematic review and meta-analysis (Figure 1). There were three retrospective studies, one prospective study, and one case series.

This systematic review included an adult population of 8,608 patients. Of these, 2,907 (33.77%) used some form of chemoprophylaxis while 5,701 (66.23%) did not use chemoprophylaxis (Table 1).

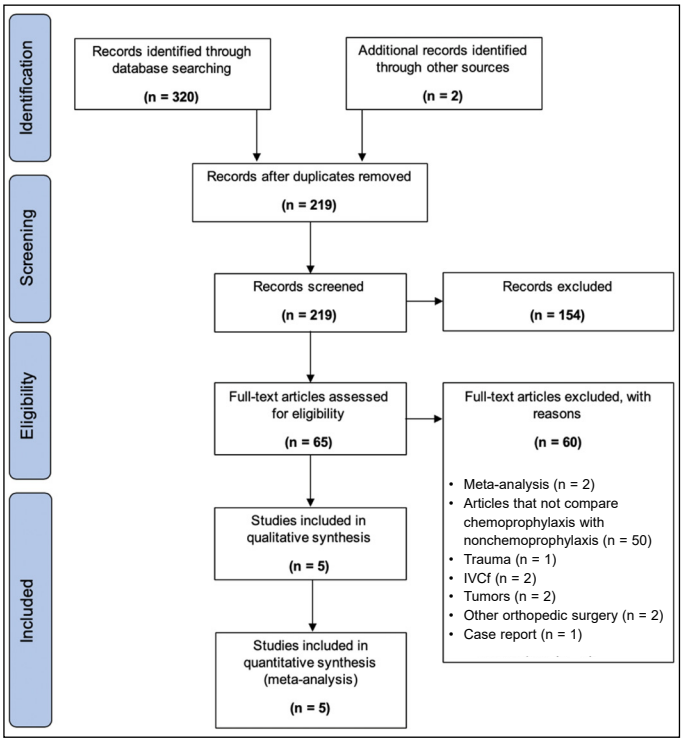

Figure 1. PRISMA flowchart of literature search

The mean age was 53.5 years, with a slight predominance of male patients (52.7%) (Table 2). There was a total of 200 DVT events, 135 of which occurred in patients where chemoprophylaxis was used and 65 where other prophylactic methods were used.

Data analysis showed that 4.64% of patients who used chemoprophylaxis had an unfavorable DVT outcome, while 1.14% of patients without chemoprophylaxis developed DVT following elective spine surgery. The data retrieved were included on a forest plot in accordance with the randomized risk ratio, showing a tendency against the use of chemoprophylaxis for DVT prevention in elective spine surgery (M-H, Random, 95%CI, 1.79 [1.26,2.55]. Test for overall effect: Z = 3.22 (P = 0.001)) (Figure 2).

Various procedures were used as non-drug prophylaxis in the studies included in the meta-analysis. Elastic compression stockings were used in the studies conducted by Rokito et al.,[15] Nicol et al.[16] and Weber et al.[17] Pneumatic compression boots were used by patients not receiving chemoprophylaxis in the studies conducted by Nicol et al.[15] and Weber et al.[16] Patients not receiving chemoprophylaxis in the study conducted by Yang et al.[8] were given non-specified mechanical prophylaxis. Only the study conducted by Dhillon et al.[11] did not specify the procedure for patients who did not have chemoprophylaxis. The studies that used elastic stockings as a non-pharmaceutical prophylaxis strategy had significantly positive outcomes, with 0% DVT following spine surgery in the study undertaken by Rokito et al.[15] and 0.29% DVT among patients in the study conducted by Nicol et al.[16]

Only three (0.1%) of the patients who received chemoprophylaxis developed epidural hematoma, and two (0.04%) of those who received non-pharmaceutical prophylaxis also had this outcome, although it was not statistically relevant (p=0.11). The studies conducted by Yang et al. and Nicol et al. did not report on the development of epidural hematoma.[16,11] Another secondary result analyzed was pulmonary thromboembolism (PTE). Eleven patients (0.38%) in the chemoprophylaxis group developed PTE, while 24 patients (0.42%) in the non-chemoprophylaxis group developed PTE (p=0.45).

DISCUSSION

Thromboembolic events in spine surgery are not a common complication but, nevertheless, they are a possible cause of mortality and morbidity.[11] When they do occur, they are associated with diverse risk factors, as reported by Al-Dujaili et al.[18] and Caprini et al.[19]: BMI > 25 Kg/m^2, advanced age, bedriddenness, history of malignant neoplasm, long-duration surgery, prior history of DVT, spinal cord injury, trauma, pregnancy, and thrombophilia. In the present review, we have also observed that, in general, patients with these risk factors have a greater chance of developing thromboembolic events after spine surgery.

Although many subspecialties have robust protocols for chemoprophylaxis following elective surgery, there is no widely accepted standard for spine surgery.[16] There is no consensus on recommendations as to when pharmaceutical prophylaxis should be used, for how long it should be used, specific complication risks – such as of epidural hematoma, or regarding DVT incidence in different populations.[16,20] Therefore, a consensual recommendation

Table 1. Study design, type of prophylaxis, and number of events.

Study (Author)	Design	Sample size	Chemoprophylaxis	n	DVT	PE	EH	Non-chemoprophylaxis	n	DVT	PE	EH
Rokito et al.[15]	Prospective study	77	Coumadin 10 mg + CS	35	0	0	0	CS	42	0	0	0
Nicol et al.[16]	Retrospective study	1111	Aspirin 150mg/day or LMWH (if aspirin is contraindicated) + CS + SCD	414	1	0	NR	SCD and/or CS or Nothing	697	2	0	NR
Weber et al.[17]	Single-center case series study	107	LMWH + CS + SCD	40	0	0	0	SCD and CS	67	2	2	0
Yang et al.[8]	Retrospective case cohort study	807	LMWH (4100UI/day)	721	97	0	NR	"Mechanical"	86	7	0	NR
Dhillon et al.[11]	Retrospective study	6506	5000 U of Heparin or 40 mg of Enoxaparin or 2500 - 5000 U of Dalteparin, or 2.5 mg of Fondaparinux	1697	37	11	3	"Non-chemoprophylaxis"	4809	54	22	2

Abbreviations: CS, Compression stockings; DVT, Deep Vein Thrombosis; EH, Epidural Hematoma; LWMH, Low molecular weight heparin; NR, Not reported; PE, Pulmonary Embolism; SCD, Sequential Compression Device.

Table 2. Study characteristics, diagnostic method, and type of surgery.

Study (Author)	Year	Country	Mean Age (Years)	Male	Female	DVT exam	PE exam	Type of surgery
Rokito et al.[15]	1996	USA	45	≈40%	≈60%	US	NR	Cervical, thoracic, or lumbar - Anterior and/or posterior spinal fusions and/or decompressions
Nicol et al. [16]	2009	Scotland	NR	NR	NR	US	NR	Laminotomy, decompression and disc enucleation + posterolateral spinal fusion, with or without decompression or pedicular fixation
Weber et al.[17]	2014	Australia	≈58	≈42%	≈58%	US	CTPA	Laminectomy and insertion of pedicle screws
Yang et al. [8]	2015	China	≈55.25	NR	NR	US	NR	Interbody fusion and fixation, single level, double level, ≥3 levels
Dhillon et al.[11]	2017	USA	≈55.78	≈53%	≈47%	NR	NR	Cervical, thoracic, lumbar, or other; whether a fusion and/or decompression (laminectomy or laminotomy) was part of the procedure

Abbreviations: CTPA, Computed tomography pulmonary angiogram; US, Ultrasound; DVT, Deep vein thrombosis; NR, Not reported; PE, Pulmonary embolism.

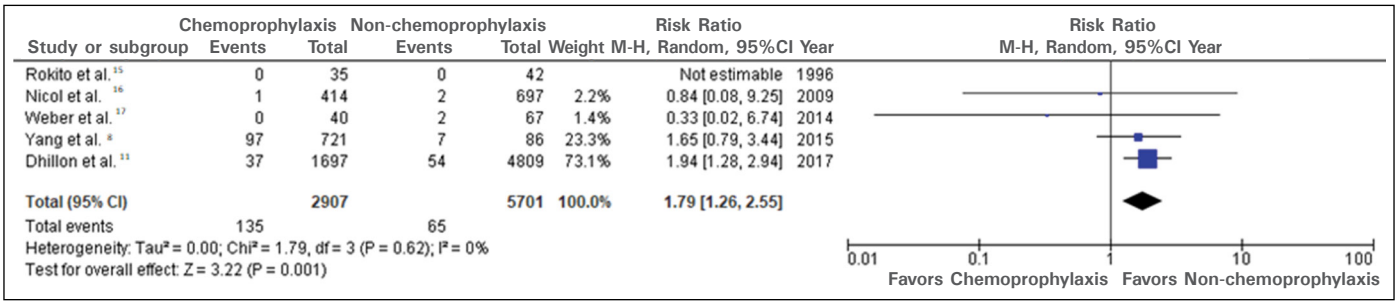

Figure 2. Forest plot showing the incidence of DVT by prophylaxis type.

based on a systematic review of clinical trials with well-defined protocols is necessary to compare the results as well as the medications and doses used.

On one hand, there are authors who advocate routine use of chemoprophylaxis, given that the risk of hemorrhagic complications does not outweigh the risk of DVT, which, in theory, is more likely to occur and has a higher morbidity and mortality rate.[16–18] On the other hand, most of the medical literature covering this discussion states that chemoprophylaxis should be rationalized with precise and restricted indications, using protocols to select patients with higher risk of DVT.[15–17]

Although the risks of adverse events due to the use of chemoprophylaxis are low, the present review found that the benefit of chemoprophylaxis in spine surgery is not clear, and therefore restricted to use in thromboembolic event risk situations, such as BMI > 25 Kg/m^2, smoking, previous thromboembolic events, malignancy, and spinal cord injury.

The study by Nicol et al.,[16] found that the overall rate of thromboembolic events was 0.27%. In the groups that used chemoprophylaxis and mechanical prophylaxis, the VTE rate was 0.24%. This difference is not statistically significant. The authors emphasize that pharmacological prophylaxis was not used more often than intermittent pneumatic compression methods, elastic stockings, or early ambulation. They point out that the position on the operating table may be an important factor for the occurrence of DVT or PTE, and suggest that the kneeling prone position would reduce the risk of such events.[16] It´s again showing that simple measures such as early ambulation, elastic stockings, and mechanical prophylaxis may be sufficient in patients at low risk for thromboembolic events after spine surgery.

Following the same line of reasoning, the study by Rokito et al.[15] concluded that the use of chemoprophylaxis methods to prevent DVT or PTE is not effective. Analysis of the data collected by these authors allowed them to identify a greater risk of hemorrhagic and compression complications, such as epidural hematoma and cauda equina syndrome, although not statistically significant. For this reason, the authors do not recommend the use of pharmacological prophylaxis in patients submitted to elective spine surgery, except in cases where there is a clear indication.[15] The greater risk of epidural hematoma noted by Rokito et al. was not corroborated by the present study, as the results of the overall adverse event risk analysis were different.

Gruber et al.,[20] found that there was no statistical difference in relation to intraoperative bleeding between the group that used preoperative chemoprophylaxis and the group that did not. This fact raises a question about the real risk of postoperative bleeding or compression complications in patients using chemoprophylaxis as a complementary prevention method in elective surgery.[20]

The study developed by Rojas-Tomba[21] defends another approach. These authors analyzed patients who did not use any prophylactic method, whether chemical or mechanical, to prevent VTE. This was justified by the fact that elective spine surgery has a low percentage of thromboembolic outcomes, and as such, costly measures such as mechanical or pharmacological compression would not need to be routinely incorporated. The authors emphasize that prophylaxis would be necessary in selected cases.[21] In fact, not using any prophylaxis method in elective spine surgery may be the practice of most spine surgeons, as confirmed by a questionnaire sent to orthopedists and neurosurgeons.[22]

From yet another perspective, some authors believe that pharmacological prophylaxis is the best method for preventing VTE in elective spine surgeries, given that the risk of hemorrhagic complications is minimal and that there is an evident benefit for prevention of thromboembolic events when low molecular weight or unfractionated heparin is administered. Strom et al.,[23] were able to demonstrate that administering chemoprophylaxis between 24 and 36 hours after surgery has a very low risk of bleeding when correctly indicated. These authors reaffirm that using compression prophylaxis in isolation is less effective than chemoprophylaxis in association with mechanical prophylaxis, and that the latter procedure should be considered for all patients who spend more than one day in the hospital, especially those who have DVT and PTE risk factors. These patients should also be routinely checked for DVT, given that, even with double prophylaxis, the chances of developing a thromboembolic event are great.[23] Although not supported by this systematic analysis, the option of short-term use can not be discarded. Therefore, an analysis of the time of chemoprophylaxis use could be addressed in future studies, comparing the differences in relation to primary and secondary outcomes.

In a recent study, Dhillon et al.,[18] found that the group using chemoprophylaxis developed a higher percentage of VTE cases as compared to the group that only used mechanical prophylaxis. The chemoprophylaxis group had greater intrinsic risk, and

pharmacological prophylaxis itself did not ensure prevention of such events. According to these authors, the risk of epidural hematoma increased in patients using chemoprophylaxis. Despite these considerations, the authors concluded that the likelihood of VTE increases up to the third postoperative day and that the use of chemoprophylaxis did not significantly increase the risk of epidural hematoma.[18]

The study by Cunningham et al.,[24] reports that DVT rates in elective spine surgery vary between 0.3% and 31%, PTE rates vary between 0.2% and 0.9%, and that epidural hematoma rates are approximately 0.1%. In our study, the results demonstrated that among patients who did not receive chemoprophylaxis, DVT was an outcome in only 1.14% of cases. Mosenthal et al.,[10] in their systematic review and meta-analysis, reported an incidence rate of 1% for the same event. However, PTE incidence among the same patients was 0.81%, which practically corresponds to twice the rate found in our study (0.42%), probably because it involved patients with more risk factors. Our results showed 4.64% DVT in patients submitted to pharmacological prophylaxis, which corresponds to almost twice that found by Du et al.,[25] where DVT incidence was 2.1% in patients submitted to anticoagulation treatment. Overall, the data produced by our study were close to those found in diverse publications in the literature.[26–29]

One of the biases of the present study was the scarcity of prospective randomized clinical trials for analysis. In addition, it was not possible to perform an independent analysis of each outcome, such as DVT, PTE, and epidural hematoma, due to the small number of cases, so the forest plot graphs were not divided by outcome.

CONCLUSION

Chemoprophylaxis was not found to be beneficial for preventing DVT when compared to non-chemoprophylaxis in adult patients having elective spine surgery.

Chemoprophylaxis did not increase the risk of postoperative epidural hematoma.

Mechanical prophylaxis can be used in patients who will stay in bed for more than one day, with the same effectiveness as chemoprophylaxis.

Chemoprophylaxis should be reserved for patients with clear risk factors for DVT or with a previous history of thromboembolic events.

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Registration

We conducted a systematic review of RCTs published through December 2019 with no language restriction. We registered a protocol for this study based on CNS Resolution 510/2016 CEP/CONEP and developed systematic search strategies for the following electronic databases: MEDLINE/PubMed, BVS (Biblioteca Virtual da Saúde), BINACIS – AR, IBECS – ES, LILACS, and Cochrane Central Register.

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