COMPARAÇÃO ENTRE QUIMIOPROFILAXIA E NÃO-QUIMIOPROFILAXIA PARA TROMBOSE VENOSA PROFUNDA EM CIRURGIA ELETIVA DE COLUNA: REVISÃO SISTEMÁTICA E META-ANÁLISE

COMPARACIÓN DE QUIMOPROFILAXIS Y NO QUIMOPROFILAXIS PARA TROMBOSIS VENOSA PROFUNDA EN CIRUGÍA ELECTIVA DE LA ESPINA: REVISIÓN SISTEMÁTICA Y META-ANÁLISIS

COMPARISON OF CHEMOPROPHYLAXIS ANDNONCHEMOPROPHYLAXIS FOR DEEP VEIN THROMBOSIS IN ELECTIVE SPINE SURGERY:SYSTEMATIC REVIEW AND META-ANALYSIS

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**RESUMO**  
  
Objetivo: Comparar quimioprofilaxia e não quimioprofilaxia 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 na análise final para fazer parte desta revisão sistemática e metanálise, sendo 3 estudos retrospectivos, 1 prospectivo e 1 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, nem aumentou o risco de hematoma epidural ou eventos tromboembólicos fatais.

Palavras-chave: Quimioprevenção; Trombose venosa; Trombose; Embolia pulmonar; Hematoma epidural; Anticoagulantes; Coluna vertebral; Fusão espinhal; Revisão sistemática; Meta-análise;

**ABSTRACT**

Objective: To compare chemoprophylaxis and nonchemoprophylaxis in elective spine surgery in order to determine risks of DVT, PTE and epidural hematoma (EH) in both groups, as well as their respective treatment efficacy. Methods: Systematic review and meta-analysis based on systematically searched articles, using combinations of MESH terms related to chemoprophylaxis and nonchemoprophylaxis for prevention of deep vein thrombosis and pulmonary embolism in elective spine surgery. Adult patients were eligible for inclusion in the study, except those with trauma, spinal cord injury, neoplasms and those using vena cava filters. Results: Five studies were included in the final analysis to form part of this systematic review and meta-analysis being 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-drug prophylaxis, 0.04% had EH (p=0,11) and 0.42% had PTE (p=0,45). Conclusions: No benefits were found for chemoprophylaxis when compared to nonchemoprophylaxis for preventing DVT in elective spine surgery, nor did it increase the risk of epidural hematoma or fatal thromboembolic events.

Keywords: Chemoprevention; Venous Thrombosis; Thrombosis; Pulmonary Embolism; Epidural Hematoma; Anticoagulants; Spine; Spinal Fusion; Systematic Review; Meta-Analysis.

**RESUMEN**

Objetivo: Comparar la quimioprofilaxis y la no quimioprofilaxis en la cirugía de columna electiva para determinar los riesgos de TVP, TEP y hematoma epidural (HE) en ambos grupos, así como su 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 de columna electiva. Los pacientes adultos fueron elegibles para su inclusión en el estudio, excepto aquellos con trauma, lesión de la médula espinal, neoplasias y aquellos que usan filtros de vena cava. Resultados: se incluyeron cinco estudios en el análisis final para formar parte de esta revisión sistemática y metanálisis sendo 3 estudios retrospectivos, 1 prospectivo e 1 série de casos. El análisis de los datos mostró 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 usan quimioprofilaxis, solo el 0.1% desarrolló hematoma epidural y el 0.38% desarrolló TEP. Entre los que recibieron profilaxis no farmacológica, el 0.04% tenía HE (p = 0.11) y el 0.42% tenía 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, ni aumentó el riesgo de hematoma epidural o eventos tromboembólicos fatales.

Palabras clave: Quimioprevención; Trombosis venosa; Trombosis; Embolia pulmonar; Hematoma epidural; Anticoagulantes; Columna vertebral; Fusión espinal; Revisión sistemática; Metanálisis;

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**INTRODUCTION**

Venous thromboembolism (VTE) is a possible complication in spine surgery, including deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE). The main risk factors are related to the components of Virchow’s triad – stasis of blood flow, endothelial injury and hypercoagulability1 –, which makes itself evident 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 33.4% accounting for PTE and 66.6% for DVT, with mortality rates of 12% and 6%, respectively, in the first month.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

Within orthopedic surgery, there is a considerable debate between 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 US shows that in lumbosacral spinal procedures, the lowest quoted rates are 0.6% for DVT and 0.3% for PE.17

Regarding spine surgery the discussion is divided between two basic issues. On one hand, the need exists to prevent complications which mainly involve thromboembolic phenomena, such as PTE, which can lead to death, and affect some 5% to 15% of patients not treated for DVT.8 On the other hand, chemoprophylaxis tends to result in greater risk of epidural bleeding in the postoperative period, which may cause neurologic symptoms and the need for emergency decompression. There are few clinical studies with high level of evidence about quimioprophilaxys for prevention DVT in spine surgery10.

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 during the first three postoperative days and anticoagulation therapy from one day before to three days after is safe for patients at high risk for VTE.18 This data has led some departments to adopt a non-chemoprophylaxis strategy, with compressive 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, determining the risks of the primary events of deep vein thrombosis (DVT) and pulmonary thromboembolism (PTE) and as secondary events of the epidural hematoma (EH), 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 intend to define possible 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)11, Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement12 and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).13 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 use of chemoprophylaxis with use of nonchemoprophylaxis 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 correlated data on surgical oncology (primary or secondary tumor), trauma, patients using vena cava filters or with neurological damage for whom data could not be separated, as well as excluding 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 for all authors and after discussed in group for consensus. Once duplicated articles were removed, two of the authors independently reviewed titles and abstracts in order to determine which studies met the inclusion criteria. Doubts and disagreements about selection were discussed with a third author. Following 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; number of cases with deep vein thrombosis (DVT), pulmonary thromboembolism (PTE) and epidural hematoma (EH) in the two groups studied. 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 have 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 (I²). Coefficient correlation and a 95% confidence interval were used on a Forest plot in order to report intensity of individual correlation and result correlation.

**RESULTS**

Out of 322 studies initially selected, 103 were removed for being duplicated 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 reading 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.

Figure 1.

This systematic review included an adult population of 8608 patients. Of these, 2907 (33.77%) used some form of chemoprophylaxis while 5701 (66.23%) did not use chemoprophylaxis (Table 1). The mean age was 53.5 years, with a slight majority of male patients (52.7%) (Table 2). There were a total of 200 DVT events, where 135 patients used chemoprophylaxis, while 65 used other prophylactic methods.

Table 1.

Table 2.

Data analysis showed that 4.64% of patients who used chemoprophylaxis had an unfavorable outcome in relation to DVT, while 1.14% of patients without chemoprophylaxis developed DVT following elective spine surgery. The data retrieved was 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).

Diverse 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.14, Nicol et al.15 and Weber et al.16  Pneumatic compression boots were used by patients not using chemoprophylaxis in the studies conducted by Nicol et al.15 and Weber et al.16 Patients not using chemoprophylaxis in the study conducted by Yang et al.17 used unspecified mechanical prophylaxis. Only the study conducted by Dhillon et al.18 did not specify the procedure for patients who did not have chemoprophylaxis. The studies that used elastic stockings as a non-drug prophylaxis strategy had significantly positive outcomes, with 0% DVT following spine surgery in the study undertaken by Rokito et al.14 and 0.29% DVT among patients in the study conducted by Nicol et al.15

Only three patients (0.1%) of those who used chemoprophylaxis developed epidural hematoma, and two (0.04%) of those who used non-drug 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 development of epidural hematoma.15,17 Another secondary result analyzed was pulmonary thromboembolism (PTE): 11 patients (0.38%) on the group using chemoprophylaxis developed PTE, while 24 patients (0.42%) who did not use chemoprophylaxis developed PTE (p=0.45).

Figure 2.

**DISCUSSION**

Thromboembolic events in spine surgery are not a common complication but nevertheless they are a possible cause of mortality and morbidity.18 When they do occur, they are associated with diverse risk factors, as reported by Al-Dujaili et al.19 and Caprini et al.20: BMI > 25 Kg/m², advanced age, bedridden, history of malignant neoplasm, long-duration surgery, prior history of DVT, spinal cord injury, trauma, pregnancy and thrombophilia. In the present revision we have also observed that patients with this risk factors have more chances to develop thromboembolic events after spine surgery in general.

Although many subspecialties have robust protocols for chemoprophylaxis following elective surgery, there is no widely accepted standard for spine surgery.15 There is no consensus on recommendations as to when drug prophylaxis should be used, for how long it should be used, specific risk of complications – such as epidural hematoma – nor regarding DVT incidence in different populations.15,21 Therefore it is necessary a consensual recommendation based on systematic review of clinical trials with well defined protocols to compare the results as the same medications and doses.

On one hand there are authors who defend that chemoprophylaxis should be used routinely, given that risks of hemorrhagic complications do not outweigh risk of DVT, which, in theory, would be a complication that is more likely to happen 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 indication, using protocols to select patients with higher risk of DVT.14–16

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, therefore being restricted to use in situations of risk for thromboembolic events such as BMI > 25 Kg/m², smoking, events previous thromboembolic events, malignancy, spinal cord injury.

The study by Nicol et al15 found that the overall rate of thromboembolic events was 0.27%. In the group that used chemoprophylaxis as well as mechanoprophylaxis in particular, the VTE rate was 0.24%; this difference was not statically significant. The authors emphasize that pharmacological prophylaxis was not used more than intermittent pneumatic compression methods, use of elastic stockings and early ambulation. They pointed out that the position of the operating table may be an important factor for DVT or PTE occurrence, and suggested that the kneeling prone position would reduce the risk of such events.15 Again showing that simple measures such as early ambulation, elastic stockings and mechanoprophylaxis 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. 14 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 greater risk of hemorrhagic and compression complications, such as epidural hematoma and cauda equina syndrome, despite not being statistically relevant. For this reason, the authors do not recommend use of drug prophylaxis in patients submitted to elective spine surgery, except in cases where there is clear indication.14 Despite the statement by Rokito et al about the great risks of epidural hematoma, this was not corroborated by the present study, presenting different results in the global analysis of the risks of adverse events.

Gruber et al.21 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 questions the real risk of postoperative bleeding or compression complications in patients using chemoprophylaxis as a complementary prevention method in elective surgery.21

The study developed by Rojas-Tomba22 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; as such, costly measures such as mechanical or pharmacological compression would not need to be incorporated as a routine. The authors emphasize that in selected cases prophylaxis would be necessary.22 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 neurosurgeons30.

From yet another perspective, some authors believe that pharmacological prophylaxis is the best method for preventing VTE in elective spine surgeries, given that 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 to 36 hours after surgery has very low risk of bleeding when correctly indicated. These authors reaffirm that using compression prophylaxis in isolation is less efficacious than chemoprophylaxis in association with mechanoprophylaxis and that the latter procedure should be considered for all patients who spend more than one day in 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, it is not possible to discard its use for short periods. Therefore, an analysis of the time of use of chemoprophylaxis 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 in comparison with the group that only used mechanoprophylaxis. 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 use of chemoprophylaxis did not significantly increase risk of epidural hematoma.18

The study by Cunningham et al.24 reports that DVT rates in elective spine surgery varies between 0.3% and 31%, PTE rates varies 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 use chemoprophylaxis, DVT was an outcome in only 1.14% . Mosenthal et al.10, in their systematic review and meta-analysis, found 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 low 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 nonchemoprophylaxis in adult patients having elective spine surgery.

Chemoprophylaxis did not increase the risk of postoperative epidural hematoma.

Mechanoprophylaxis can be used in patients who will stay in bed for more than one day, with the same efficacy 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 until December 2019, with no language restriction. We don´t registered a protocol to this study based on the resolution CNS 510/2016 CEP/CONEP and developed search strategies for the following The electronic databases: MEDLINE/Pubmed, BVS (Biblioteca Virtual da Saúde), BINACIS – AR, IBECS – ES, LILACS and Cochrane Central Register were systematically searched

**CONFLICT OF INTEREST**

All authors declare no potential conflict of interest related to this article.

**CONTRIBUTION OF THE AUTHORS**

Each author made significant individual contributions to this manuscript. BLC (0000-0002-1149-5446)\*: structuring, data analysis and writing; CCB (0000-0002-0986-8979)\*: structuring, data analysis and writing; GWR (0000-0002-2525-8820)\*: structuring, data analysis and writing; LAFMG (0000-0001-8471-7903)\* structuring, data analysis and writing; SZK (0000-0001-8471-7903)\* structuring, data analysis and statistical analysis; FBT (0000-0003-3330-7837)\*: intellectual concept, structuring, data analysis and writing; ENV (0000-0003-1157-4889)\*: intellectual concept, data analysis and revision; LRGV(0000-0002-0638-4311)\*: intellectual concept, data analysis and revision; \*ORCID (*Open Researcher and Contributor ID*).”

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