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Pulmonary embolism prophylaxis with inferior vena cava filters in trauma patients: a systematic review using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines

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Abstract Prophylactic inferior vena cava filters (pIVCFs) for the prevention of pulmonary embolism (PE) are controversial. Current practice guidelines (EAST and ACCP) are based on the critical appraisal of observational studies. As a result, their recommendations are conflicting and may account for practice pattern variation. The purpose of this study is to critically review the available literature and ascertain the level of evidence both for and against the use of pIVCFs for PE prophylaxis in trauma patients. We searched PubMed and Web of Science for publications from 1950 until July 2010 that assessed the efficacy of PE prevention with pIVCFs in the trauma population. We followed the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for design, implementation, and reporting. The Newcastle-Ottawa Score was used for quality and comparability assessment. Seven observational studies met inclusion criteria for this meta-analysis, representing 1,900 patients. Only one study was published in this decade. The rate of PE was statistically lower in the IVCF group compared to a matched control group without IVCFs (OR 0.21, 95% CI 0.09–0.49). There was no significant difference in DVT. Using the MOOSE criteria these results show a decreased likelihood of PE among trauma patients who receive pIVCFs. Although these results could favor the placement of pIVCFs, the lack of contemporary use of pharmacologic prophylaxis across studies does not allow us to make firm conclusions either for or against the routine use of pIVCFs. Prospective randomized trials are needed to determine the role of pIVCFs in high-risk trauma patients.

Keywords Inferior vena cava filters · Venous thromboembolism · Trauma · Pulmonary embolism · Review

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Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a leading cause of morbidity and mortality in trauma patients. Accepted indications for the use of inferior vena cava filters (IVCFs) include patients with known VTE in whom anticoagulation is contraindicated, patients with recurrent PE despite adequate anticoagulation, and those in whom there has been a complication from anticoagulant therapy [1]. While there is a growing interest in retrievable filters as a method of thromboprophylaxis, existing evidence-based guidelines for prophylactic IVCFs (pIVCFs) are conflicting and may account for varying practice patterns amongst major trauma centers in the United States. In 2002, the Eastern Association for the Surgery of Trauma

(EAST) cited class III evidence (retrospective data, expert opinion, or case report) to support the use of pIVCFs in high-risk trauma patients [2]. In contrast, the 2008 American College of Chest Physicians (ACCP) guidelines on the prevention of VTE recommended against the use of IVCF as primary prophylaxis in trauma patients based on Grade IC evidence (strong evidence based on observational studies) [3]. The literature on the efficacy of pIVCFs in trauma patients without VTE is controversial [4–18]. To date, there have been no randomized controlled trials addressing the efficacy of IVCFs as VTE prophylaxis in any patient population.

We sought to evaluate the current literature on pIVCFs as VTE prophylaxis in high-risk trauma patients to determine the evidence for or against pIVCF placement. Since no randomized controlled trials exist, this systematic review and meta-analysis is based on observational studies. We employed the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria to report our meta-analysis of observational studies and determine the weight of the existing literature regarding the use of pIVCFs in trauma patients [19].

Methods

All steps of the literature search, study identification, study selection, quality assessment, and data extraction were done independently by two investigators of different subspecialties, hematology and trauma surgery (AR and DA). Disagreements were resolved by discussion, and consensus was achieved in the selection of articles for analysis. Inter-rater agreement k statistic was 0.81 [20]. We followed the MOOSE guidelines during stages of design, implementation, and reporting of this meta-analysis [19]. This proposal provides a checklist for authors, reviewers, editors and readers for reporting outcomes of meta-analyses based on observational studies. The MOOSE recommendations delineate specifications for reporting background, search strategy, methods, results, discussion, and conclusion.

Study identification

We searched two electronic databases, PubMed and Web of Science, for papers published from the earliest available online year of indexing until July 2010 that assessed the role of pIVCFs in the trauma population. We subsequently cross-referenced bibliographies of each article and textbooks to identify further relevant studies [21, 22]. When details of studies were in question, we contacted the authors of these studies. When searching PubMed we used the keywords "trauma", "venous thromboembolism", and "vena cava filter". No limits on language or location were placed. When searching Web of Science we used the keywords "clinical trial or clinical study", "inferior vena cava filters", and "trauma". Potential relevant studies were screened for retrieval. After inclusion and exclusion criteria were applied a comprehensive list of relevant articles were included in the systematic review.

Study selection

The abstracts of all articles were reviewed for the following inclusion criteria: (1) patients with filters placed for prophylactic indications, i.e. prior to any known VTE disease, (2) studies that compared a group with pIVCFs with a group without pIVCFs, (3) studies that included only trauma patients, (4) studies with outcomes including either symptomatic PE and/or symptomatic DVT assessed by appropriate radiologic investigation.

The following exclusion criteria were applied: (1) population included non-trauma patients, (2) case series and case reports, (3) studies that included patients with known VTE prior to IVCF placement, (4) outcome of VTE was not reported, (5) scaled score of less than four stars on the Newcastle-Ottawa scale (NOS) [23].

Quality assessment: the Newcastle Ottawa scale

Quality assessment for observational studies was carried out using the guidelines provided by the MOOSE statement. The quality of studies identified was assessed according to the study setting, completeness and duration of follow up, validity and completeness of exposure and outcome ascertainment, comparability of the control group, and adjustment for known confounding variables. Furthermore, the quality of studies in this meta-analysis was assessed using the NOS as recommended by the Cochrane Non-Randomized Studies Methods Working Group (Table 1) [23, 24]. This instrument was developed to assess the quality of nonrandomized studies, specifically cohort and case–control studies [25]. Based on the NOS cohort studies were judged based on three broad perspectives: selection of study groups (1 criteria), comparability of study groups (4 criteria), and ascertainment of outcome of interest (3 criteria). Given the variability in quality of observational studies found on our initial literature search, we considered studies that met 5 or more of the NOS criteria as high quality and therefore included only these studies in our meta-analysis [26–29].

Data extraction

Data were independently abstracted by both reviewers (AR and DA). Standardized abstraction sheets were employed for recording of data from individual studies. Key

Table 1 Quality assessment using NOS

Reference	Year	Study design	NOS quality score (maximum 9)
Gosin et al. [15]	1997	Observational cohort	7
Khansarinia et al. [5]	1995	Observational cohort	9
Rodriguez et al. [7]	1996	Observational cohort	7
Rogers et al. [9]	1995	Observational cohort	8
Rogers et al. [16]	1997	Observational cohort	7
Rosenthal et al. [17]	1994	Observational cohort	7
Gorman et al. [18]	2009	Observational cohort	8

characteristics extracted from each study and subsequently recorded in a combined evidence table included: author, year of publication, study design, study population, type of filter, adjunctive pharmacologic and mechanical prophylaxis, method of VTE detection, and study primary and secondary outcomes.

Outcomes

Primary endpoints of interest were symptomatic PE and DVT. Secondary endpoints of interest were complications of IVCF placement, filter patency rates, and filter retrieval rates, if reported.

Statistical analysis

RevMan Analyses software (RevMan 5.0) of the Cochrane Collaboration was used for this meta-analysis. The odds ratio (OR) with 95% CI was used to estimate the strength of association for dichotomous variables. Assessment of heterogeneity between trials was tested using both chi-squared test and I-squared test. Between-study heterogeneity was considered to be significant for $P < 0.10$. If there was no heterogeneity, a fixed effects model was used. If heterogeneity was found, sensitivity analysis was conducted. If the reasons that led to the heterogeneity could not be found by sensitivity analysis, a random effects model was used [30]. In addition we performed exploratory analysis comparing studies that used pharmacologic prophylaxis versus those that did not. Publication bias was examined in a funnel plot of log OR against its standard error using Begg's test, and the degree of asymmetry was tested statistically using Egger's unweighted regression asymmetry test [31, 32]. Statistical analyses were also undertaken using SAS (SAS version [9.2] of the SAS System for [Windows] Copyright @ 2002–2008 by SAS Institute Inc., Cary, NC, USA.) and Review Manager (RevMan) [Computer program] Version 5.0 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, UK, 2008).

Results

Characteristics of studies included

Of 91 potentially relevant studies screened for retrieval, 53 review articles, case reports, case series, and irrelevant studies were excluded. After retrieving 38 articles for detailed evaluation 31 studies were excluded because inclusion criteria were not met. We found no randomized controlled trials addressing the role of prophylactic IVCFs in trauma patients. Seven studies, with a total of 1,900 patients, published between 1994 and 2009 met our search criteria (Fig. 1) [5, 7, 9, 15, 18]. All seven were cohort studies that reported PE rates, two of which also report DVT outcomes [7, 18]. Three studies were prospective studies [5, 15, 16] and four were retrospective studies [7, 9, 17, 18]. Five studies were conducted at Level 1 trauma

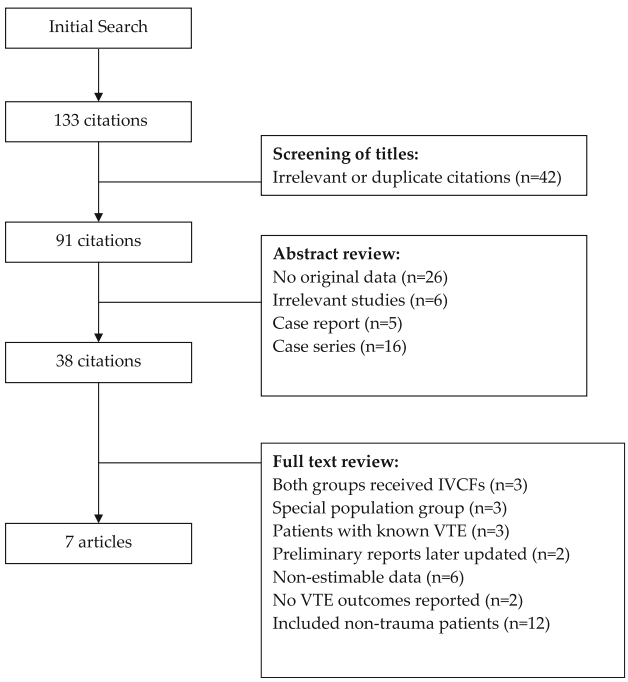

Fig. 1 QUORUM diagram of literature search

Table 2 Evidence table of included observational studies

Reference	Level 1 trauma center	Study population	Control population	IVCF	Concurrent pharmacologic prophylaxis	Outcomes	Length of follow-up
Gosin et al. [15]	Yes	HRTP	Historical	Permanent	Yes—UFH 5000u q8–12 h	PE, complications	Not reported
Khansarinia et al. [5]	Yes	HRTP	Historical	Permanent	Yes—UFH	PE, complications	Until hospital discharge
Rodriguez et al. [7]	No	HRTP	Historical	Permanent	Yes—no details	PE, DVT	Until hospital discharge
Rogers et al. [9]	Yes	HRTP	Historical	Permanent	No	PE, complications, IVCF patency	Until death or hospital discharge
Rogers et al. [16]	Yes	HRTP	Historical	Permanent	No	PE, complications, IVCF patency	1 year
Rosenthal et al. [17]	No	HRTP	Historical	Permanent	UFH 5000u q8–12 h	PE, IVCF patency	Mean 32.8 months
Gorman et al. [18]	Yes	HRTP	Retrospective concurrent	Not reported	Yes—LMWH/UFH/ or Coumadin	PE, DVT	During rehabilitation

HRTP high risk trauma patient, *PE* pulmonary embolism, *DVT* deep vein thrombosis, *LMWH* low molecular weight heparin, *UFH* unfractionated heparin

centers [5, 9, 15, 16, 18]. All seven studies were reported in the English language and were conducted in U.S. level-1 trauma centers. The average number of patients per study was 271 with a range between 112 and 755. All pIVCFs were placed either in the operating room or interventional radiology suite. Length of follow-up varied ranging from follow-up until hospital discharge to a mean follow-up of 32 months in one study (see Table 2) [17].

Study and control population

All seven cohort studies included trauma patients considered high-risk for VTE. The definition of high-risk varied marginally between studies although most studies included the ACCP or EAST definition of trauma patients high-risk for VTE [2, 3]. Controls were matched for at least one of the following: injury pattern, sex, age, ISS, risk factors for PE and therefore were also considered high-risk for VTE. Six studies specified that Greenfield permanent IVCFs were placed [5, 7, 9, 15, 17].

Concurrent VTE prophylaxis

In addition to prophylactic IVCF, pharmacologic prophylaxis (UFH or LMWH) was used in four out of seven cohort studies [5, 7, 15, 18]. Mechanical prophylaxis was used in the form of sequential compression devices (SCDs) [5, 7, 15, 17] or graduated compression stockings [18] if injury did not preclude their use. Sensitivity analyses determined that lack of pharmacologic prophylaxis did not alter overall outcome. Of the two cohort studies that reported DVT incidence neither performed surveillance for DVT and therefore all DVT's reported were symptomatic. Many patients with closed head injuries or spinal cord injuries did not receive pharmacologic prophylaxis [9, 16, 17].

Primary outcomes

Cohort studies reporting PE and DVT

We performed a meta-analysis using seven cohort studies that met the search criteria. These cohort studies reported incidence of symptomatic PE in the study population with pIVCF compared to matched controls, as described above, receiving no IVCF. The incidence of PE was statistically lower in the IVCF group (OR 0.21, 95% CI 0.09–0.49; Fig. 2). No significant heterogeneity among the cohort studies existed. Two cohort studies reporting DVT incidence showed no statistically significant difference in DVT rates between the IVCF and no IVCF groups (OR 1.6 with 95% CI 0.76–3.37, Fig. 3).

Secondary outcomes

Gosin et al. [15] reported 0% complications after IVCF placement. Khansarinia et al. [5] noted approximately 2% complication rate including an internal jugular thrombosis in a previously diseased vein and an improper filter release, which subsequently led to filter migration requiring operative removal. In one study by Rogers et al. [9] two insertion site thromboses, defined as DVT within 48 h of IVCF insertion, and two asymptomatic IVCF occlusions

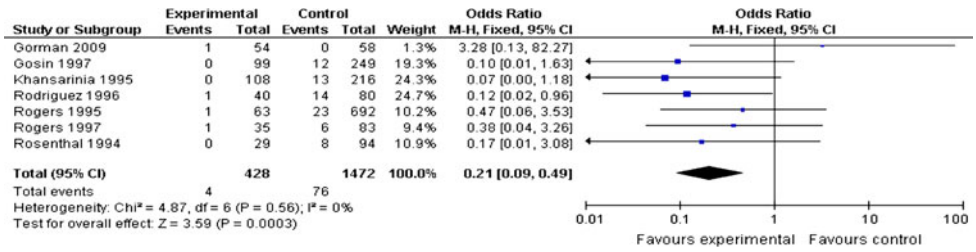

Fig. 2 Cohort studies reporting PE

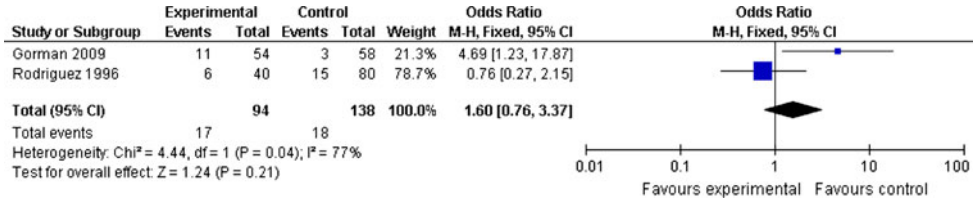

Fig. 3 Cohort studies reporting DVT

developed. A subsequent study by Rogers et al. [16] reported approximately 6% insertions site thrombosis and 3% tilt complication rate.

Three studies reported IVCF patency rates while no studies reported retrieval rates. At mean follow-up of 32 months, Rosenthal et al. [17] noted 100% patency rates of IVCFs. Both studies by Rogers and co workers [9, 16] published 100% 30 day patency rate and over 90% 1-year and 2-year patency rate.

Discussion

Practice patterns regarding the placement of pIVCFs in trauma patients vary. The 2002 EAST guidelines cite retrospective data, expert opinion, or case report to support the use of pIVCFs in high-risk trauma patients while 2008 ACCP guidelines recommend against the use of pIVCFs in trauma patients [2, 3]. However, in performing this systematic review and meta-analysis we note that even among the higher quality observational cohort studies, the primary limitation of these older studies is the inconsistent use of appropriate pharmacologic prophylaxis. Practice patterns have changed with respect to pharmacologic prophylaxis in 2010. The current standard of practice for pharmacologic prophylaxis in trauma patients is low-molecular weight heparin, typically enoxaparin 30 mg subcutaneously twice daily, based on two randomized controlled trails published in 1996 [33, 34]. In this review, more than half of the studies were published in the era prior to 1996 when LMWH was not the standard of VTE prophylaxis. Only one study was published recently in 2009 and even in this study, prophylaxis was not standardized (LMWH, UFH, or Coumadin) [18].

With these limitations in mind, we performed a meta-analysis to weigh the results of the pooled data based on both contemporary and previous studies used to develop the EAST and ACCP guidelines. Such an analysis may add to the interpretation of the collective body of literature. There was a statistically significant decrease in PE with pIVCF placement among the cohort studies (OR 0.21, 95% CI 0.09–0.49). This illustrates how the pooled data may provide a different result since, individually, nearly all of the cohort studies did not show significance. The exception was the cohort study by Rodriguez et al. which demonstrated a significant reduction in PE incidence in the IVCF group compared with a control group without IVCF (2.5% versus 17%) matched for mechanism of injury and risk factors for PE [7]. The risk of DVTs among the pIVCF group is less clear. There were only two cohort studies that met our criteria for meta-analysis. There was a trend towards an increased incidence of DVTs, OR 1.6 (95% CI 0.76–3.37) in the IVCF group.

There are several limitations of this study. While the methodological quality of observational studies is suboptimal when compared to randomized controlled studies, the number of published meta-analyses of observational studies has increased [35]. Meta-analysis of observational studies can be a useful adjunct to a systematic review, when generalizations have been made on a collective body of existing studies. Some aspects of power, heterogeneity, and bias can be addressed with stringent methods such as those employed by the MOOSE criteria [19]. The MOOSE methodology has been accepted by epidemiologists as an alternative when there is a lack of randomized controlled trials, yet there is an abundance of observational studies of similar design.

As mentioned previously, most studies were published prior to the era that LMWH was established as the standard of pharmacologic prophylaxis. More recent studies may have employed pharmacologic prophylaxis but this was either not documented or not standardized in terms of dose, time of initiation, or length of extended prophylaxis [5, 7, 15, 18]. This variation could account for why our sensitivity analysis showed that lack of pharmacologic

prophylaxis did not alter PE incidence. Similarly SCD use was mentioned in many articles as adjunctive VTE prophylaxis but compliance rate was not documented [5, 7, 15, 17]. The consistent evidence of poor compliance with proper use of SCDs by patients and nursing staff is a major limitation of SCDs [36]. We contacted all authors for clarification and details of VTE and SCD prophylaxis the results of which are reported in Table 2. The timing of VTE outcome could also serve as another potential confounder. Since it is accepted that PE is the third most common cause of in hospital death in trauma patients surviving the first 24 h, timing of VTE outcome may not be an issue in this review because patients in each study were followed at least until hospital discharge. There was enough follow up time to achieve either DVT or PE outcome.

Another limitation of this meta-analysis is the introduction of measurement bias. The method of diagnosis of VTE in each study was not uniform. Many studies used older techniques such as pulmonary angiogram or ventilation-perfusion scans rather than computed tomography for diagnosis of PE. Similarly, several studies used impedance phlebography (IPG) rather than Doppler ultrasounds for detection of DVT. However, clinical presentation was accounted for as we only included studies reporting symptomatic PE and/or DVT.

Finally, observational studies are likely to have significant publication bias as negative studies are frequently not reported. However it should be noted that only one study among the seven in the meta-analysis reported a significant decrease PE incidence after pIVCF placement. Thus, the argument that negative studies are not reported and that our results are only from studies that show a positive effect would not hold true in this situation. We also assessed for this potential publication bias using the Beggs-Egger's plot (Figs. 4, 5). No significant outliers were noted to weigh the final results in one particular direction.

Despite the pooled finding of a decreased incidence of PE, given the underlying limitations of the included observational studies, specifically lack of contemporary

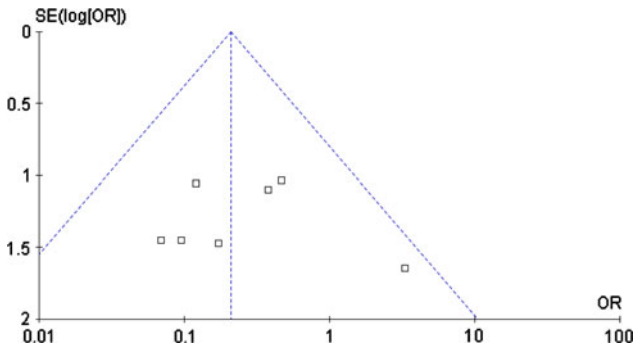

Fig. 4 Funnel plot of Cohort studies reporting PE

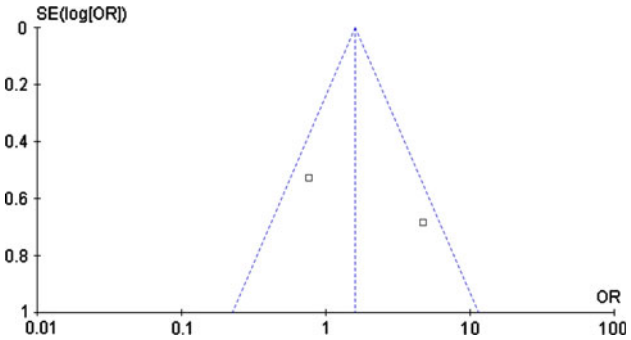

Fig. 5 Funnel plot of Cohort studies reporting DVT

pharmacologic prophylaxis, we conclude that there is insufficient evidence to routinely recommend pIVCFs in high-risk trauma patients. Well-designed prospective randomized trials are necessary to elucidate the role of pIVCFs in trauma patients.

Conclusion

We conclude that the available literature to date addressing the role of pIVCFs in trauma patients is not adequate to make recommendations either for or against the routine use of pIVCF in high-risk trauma patients. We demonstrate that a meta-analysis of observational studies using rigorous statistical methods can be performed in the setting of lack of randomized controlled trials. Clearly there are specific indications relevant to this patient population where IVCFs are appropriate and therefore the decision to place an IVCF must be made on an individual basis. However, given the lack of contemporary literature we cannot make any firm conclusions regarding the placement of pVCFs in trauma patients. In addition, the studies used in this meta-analysis as well as current clinical guidelines by EAST and ACCP may not apply to current practice as the pharmacologic prophylaxis, type filters used, and the methods of diagnosis of VTE are different. Prospective randomized controlled trials are needed to determine the efficacy and safety of pIVCFs in trauma patients.

Conflict of interest All authors have no conflicts of interest to disclose.

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