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Effectiveness of Sequential Compression Devices in Prevention of Venous Thromboembolism in Medically Ill Hospitalized Patients: A Retrospective Cohort Study

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RUNNING HEAD

SCD for VTE prevention in hospitalized patients

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CONFLICT OF INTEREST

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PRIOR PRESENTATION

This paper was presented as an abstract, after preliminary data analysis, at the 59th American Society of Hematology 2017 Annual Meeting held on December 9, 2017, Atlanta, GA.

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CONTRIBUTIONS

PD developed the concept of the study. PD, LW, and JG designed the study and were involved in data analysis. All authors contributed to the interpretation of the results. The initial manuscript was drafted by PD. All authors reviewed and critically revised the manuscript. All the authors approved the final version of the manuscript.

ABSTRACT

Objective: To evaluate effectiveness of sequential compression devices (SCD) for venous thromboembolism (VTE) prevention in medically ill hospitalized patients.

Methods: Adult patients admitted to a teaching hospital from April 2015 and March 2016 were included. Patients on anticoagulants with or without SCD were excluded. We analyzed VTE risk, length of hospital stay, and other co-morbidities among propensity score-matched patients on SCD and no thromboprophylaxis (NONE).

Results: Among 30,824 patients, 67 patients (0.22%) developed VTE during the hospital stay: DVT in 55 and PE in 12. VTE was seen in 47 out of 20,018 patients on SCD (41 DVT, 6 PE) and 20 out of 10,819 patients on NONE (14 DVT, 6 PE). Risk- adjusted analysis showed no significant difference in VTE incidence in SCD group compared to NONE. (Odds Ratio 0.99, 95% Confidence Interval 0.57-1.73, p=0.74).

Conclusion: SCD, compared to NONE, is not associated with decreased VTE incidence during hospital stay.

INTRODUCTION

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), affects 1 million patients in the United States each year [1-3]. Hospitalization is a major risk factor for VTE, with 150-fold increase in risk compared to non-hospitalized individuals [2, 4]. Anticoagulants are commonly used for VTE prevention in hospitalized patients, and sequential compression devices (SCD) are recommended in combination with anticoagulants or when anticoagulants are contraindicated [5]. Current guidelines for SCD use are consensus-based, derived mostly from surgical patients by comparing the effects of SCD plus anticoagulation versus anticoagulation alone [5-8]. In routine practice, SCD is used extensively in hospital despite limited evidence in medically ill patients [6, 9]. We explored the effectiveness of SCD in medically ill hospitalized patients.

METHODS

Participants and study design

We included all patients admitted to medical inpatient service from April 2015 to March 2016 at Sparrow Hospital, a secondary care teaching hospital (Figure 1). Patients <18 years or diagnosed with VTE on admission were excluded. Patients on anticoagulants at home or at hospital were excluded to eliminate the effects of anticoagulant use. Trained investigators abstracted the data

including demographic characteristics, diagnostic methods, methods for VTE prevention, length of hospital stay (LOS), VTE events, and comorbidities. Charlson comorbidity index (CCI) was calculated. Eligible patients were divided into SCD group (only on SCD during hospital stay) and NONE group (no VTE prophylaxis during hospital stay).

Study outcomes

The primary outcome was a new diagnosis of symptomatic VTE during the hospital stay. The outcomes were confirmed with Doppler ultrasonography for DVT and computed tomography pulmonary angiogram or ventilation-perfusion scan for PE.

Statistical analysis

Differences between SCD group and NONE group were compared using t-tests or Wilcoxon rank sum tests for continuous variables, and Chi-square tests for categorical variables. Since patients were not randomly assigned to receive SCD, a propensity score analysis was performed. For each patient, we estimated the propensity score(likelihood of receiving SCD) from a multivariable logistic regression model. There are features of randomness in the selection of treated patients and their match that could lead to different models for assessing the propensity scores. We experimented with different specifications, especially for LOS and CCI with same qualitative conclusion. The variables included in the final model for propensity scores were gender, any type of cancer, comorbidities, and three continuous variables modelled by splines: age(6 terms), log-transformed LOS(3 terms) and CCI(4 terms). A spline function of a continuous variable is a smooth function composed of polynomial pieces connected at interior points called knots in the range of the variable [10, 11]. The c-statistic was 0.707 indicating an acceptable level of discrimination between SCD and NONE patients. Figure 2 depicts adjusted OR and 95% confidence intervals(CI) for the binary variables. We followed published principles and guidelines to form treated and non-treated pairs based on their propensity scores [12, 13]. A randomly chosen SCD patient was matched to one NONE patient, in the common region of propensity scores extended by 0.25 times the pooled estimate of the standard deviation of the logits of propensity scores in the two groups. This greedy matching algorithm proceeded sequentially with SCD patients selected in random order of their propensity score and matched to a unique NONE patientresulted in 10,071 unique pairs. SAS procedure PSMATCH was used for matching. In the matched sample, we examined the quality of the matching by comparing the standardized mean differences and variance ratios between SCD and NONE [14, 15]. We used conditional logistic regression to obtain the adjusted OR and 95% CI for the association of SCD with VTE incidence. We also performed a risk-adjusted analysis for VTE incidence with an indicator of SCD use. A multivariable logistic model with a subset of the covariate mix was applied using information criteria for model selection [16].

The study was determined exempt by Michigan State University and Sparrow Hospital with IRB # i051275.

RESULTS

Patient characteristics

Total 30,824 patients were included in analysis: mean age was 54±21 years, 61.5% were females. Mean CCI was 4.5±2.4. Mean LOS was 4.5±4.3 days. Out of total patients,

20,018(64.9%) were on SCD and 10,819(35.1%) on NONE. Patient characteristics, including those on anticoagulants, are depicted in Table 1.

Outcome

Sixty-seven(0.22%) patients had VTE: DVT in 55 and PE in 12. DVT and PE in SCD group were 41 and 6, compared to 14 and 6 in NONE group. About 0.23% of total patients on SCD developed VTE compared to 0.18% on NONE.

SCD impact on VTE incidence

In the unadjusted analysis, use of SCD was not associated with decreased VTE incidence(OR 1.27, 95% CI 0.75-2.14, p=0.37) (Table 2). Conditional logistic regression after propensity matching yielded an adjusted OR of 0.9(95% CI 0.47-1.7, p=0.75) for VTE incidence with SCD. Similarly, the adjusted OR for SCD after multivariable logistic regression was 0.99(95% CI: 0.57-1.73, p=0.98).

DISCUSSION

Our large retrospective study of 30,824 medically-ill patients demonstrated similar incidence of VTE with SCD only compared to NONE. SCD patients in comparison to NONE had significant differences in risk factors for VTE including higher CCI, higher prevalence of cancer and obesity, and longer LOS. Propensity score matching matched both SCD and NONE groups with no statistical difference in VTE incidence. The overall incidence of symptomatic VTE was <1% in our study which might have played a role in the results. Previous studies have reported significantly higher incidence of VTE is in critically- ill patients compared to other non-critical medically-ill patients [17-21]. Critically-ill patients on anticoagulants or both anticoagulants and SCDs were not eligible for analysis in our study which could be one of causes for lower incidence of VTE. Multiple studies also screened patients for VTE before discharge, which would lead to the diagnosis of asymptomatic VTE and subsequently, increase the overall incidence of VTE [22]. We studied symptomatic patients only and no screening for asymptomatic VTE was performed.

Despite significant results in surgical patients, existing literature has shown mixed results regarding use of SCD in medically ill patients. This could be related to publication bias in these types of study. Limpus et al. performed a systematic review on compression and pneumatic devices for thromboprophylaxis in intensive care patients [23]. Twenty-one studies with >4,000 individuals were analyzed and there was no significant difference with use of compressive and pneumatic devices compared to no treatment or use of anticoagulant [23]. In another review, the strength of evidence was insufficient to determine the effectiveness of SCD for thromboprophylaxis in high risk medical patients because of limited data [24]. CLOTS III trial reported significant effectiveness of SCD in DVT prevention in immobile patients with acute stroke. Since these patients were considerably less mobile, the results may not be reproducible in our study. Some other studies reported lower incidence of VTE with SCD compared to NONE but the results were not statistically significant [7, 25].

STRENGTHS AND LIMITATIONS

Our study should be viewed in the context of its strengths and limitations. Although the risk of VTE in hospitalized patients tends to persist for weeks after hospitalization, we focused on VTE during hospital stay, which might have led to decreased VTE incidence [26]. In fact, the number of symptomatic VTE events during hospital stay in medically-ill patients has been reported to be similar to the number of VTE after discharge [27]. However, with VTE incidence of <1%, the projected number of VTE events after discharge in our study population would still be lower than that reported in literature. Our analysis excluded high risk patients who received anticoagulants with or without SCD and may not represent all hospitalized medical patients seen in clinical practice. The compliance and appropriate use of the SCD could not be verified in all cases. However, this is one of the few analyses looking at the effectiveness of SCD in acutely ill medical patients. We matched patients from large sample size to minimize many potential confounders of association between the preventive methods and outcomes. The number of patients given anticoagulants was modest and lower that recommended by many contemporary guidelines. Our study supports scaling back current guidelines recommending widespread use of anticoagulants or SCD until better prospective evidence from randomized trials is available.

CONCLUSION

SCD, compared to NONE, was not associated with decreased VTE incidence. VTE incidence was <1% during hospital stay although asymptomatic VTE may have occurred before discharge. Strength of evidence might be insufficient to exclude clinically important differences in treatment effects because of selection bias in choice of therapy, undetermined number of VTE after discharge, and exclusion of higher risk patients on anticoagulation. Further prospective studies are needed to clarify the role of SCD in medically ill patients.

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Figure 1: CONSORT diagram for cohort selection

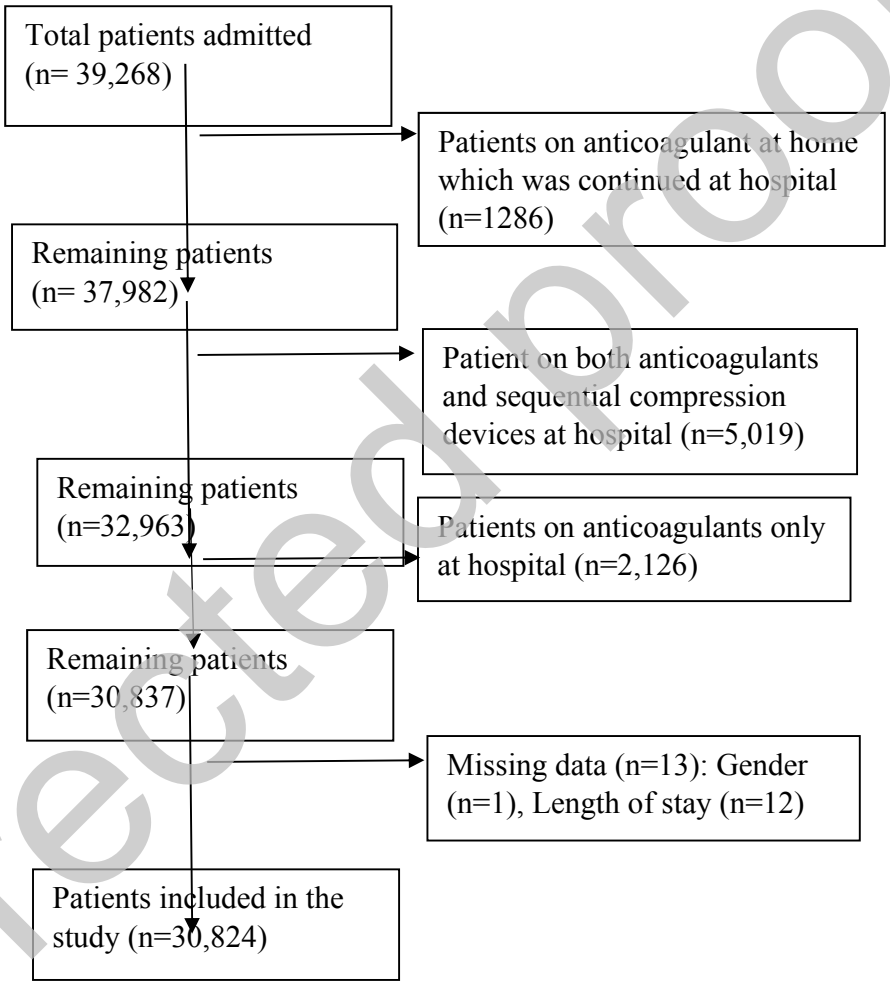
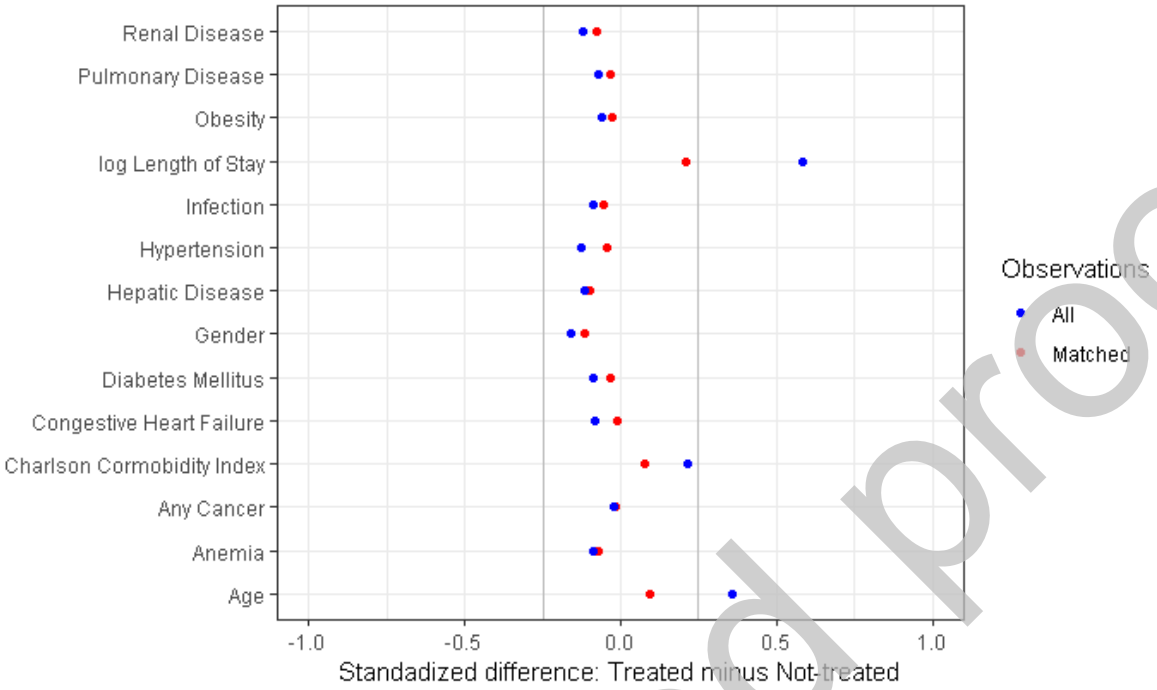


Figure 2: Standardized differences in observed variables between matched pairs



Standardized difference between SCD treated and matched non-treated is the difference in means or proportions divided by an estimate of standard deviation obtained as the square-root of the average variance in treated and non-treated groups. In the matched sample, the differences are within the ±0.25 reference lines for good variable balance.

Table 1: Patient characteristics

Variables	SCD, N=20,018	NONE, N=10,819	AC, N=2,126	BOTH, N= 5019
Age, years (Mean ± SD)	57 ± 21	49 ± 21	65 ± 16	65 ± 16
Charlson Comorbidity Index (Mean ± SD)	4.7 ± 2.4	4.2 ± 2.2	5.6 ± 2.6	5.9 ± 2.7
Length of stay, days (Mean ± SD)	4.1 ± 4.6	2.7 ± 3.5	6 ± 8	7.8 ±8.7
Gender, male (n,%)	8263 (41.3)	3623 (33.5)	1146 (53.9)	2594 (51.7)
Co-morbidities				
Infection (n,%)	1766 (8.82)	699 (6.46)	222 (10.4)	783 (15.6)
Pulmonary disease (n,%)	2958 (14.78)	1333 (12.32)	370 (17.4)	1113 (22.18)

Hypertension (n,%)	4147 (20.72)	1712 (15.82)	472 (22.2)	1112 (22.2)
Renal disease (n,%)	1698 (8.48)	588 (5.43)	297 (13.97)	1004 (20)
Diabetes (n,%)	2306 (11.52)	957 (8.85)	390 (18.34)	888 (17.69)
Congestive heart failure (n,%)	1168 (5.83)	444 (4.10)	276 (13)	819 (16.3)
Hepatic disease (n,%)	728 (3.64)	193 (1.78)	65 (3.1)	186 (3.7)
Anemia (n,%)	615 (3.07)	184 (1.70)	44 (2.07)	176 (3.51)
Obesity (n,%)	1435 (7.17)	612 (5.66)	210 (9.9)	443 (8.8)
Cancer				
Any Cancer (n,%)	545 (2.7)	145 (1.34)	55 (2.59)	183 (3.65)
Abdominal (n,%)	18 (0.09)	6 (0.06)	2 (0.09)	6 (0.12)
Brain (n,%)	23 (0.11)	1 (0.01)	0 (0)	2 (0.04)
Breast (female) (n,%)	63 (0.31)	12 (0.11)	2 (0.09)	18 (0.36)
Cervical (female) (n,%)	27 (0.13)	3 (0.03)	2 (0.1)	7 (0.14)
Colon (n,%)	30 (0.15)	7 (0.06)	1 (0.05)	7 (0.14)
Esophageal (n,%)	10 (0.05)	2 (0.02)	0 (0)	6 (0.12)
Head (n,%)	13 (0.06)	2 (0.02)	0 (0)	3 (0.06)
Hodgkin (n,%)	6 (0.03)	3 (0.03)	1 (0.05)	4 (0.08)
Leukemia (n,%)	40 (0.20)	28 (0.26)	14 (0.66)	14 (0.28)
Lung (n,%)	117 (0.58)	32 (0.30)	11 (0.52)	38 (0.76)
Lymphoma (n,%)	25 (0.12)	8 (0.07)	2 (0.09)	13 (0.26)
Myeloma (n,%)	22 (0.11)	1 (0.01)	4 (0.19)	10 (0.2)
Non Hodgkin (n,%)	34 (0.17)	16 (0.15)	5 (0.24)	17 (0.34)

Ovarian (female) (n,%)	33 (0.16)	3 (0.03)	3 (0.14)	7 (0.14)
Pancreatic (n,%)	21 (0.10)	6 (0.06)	1 (0.05)	6 (0.12)
Rectal (n,%)	27 (0.13)	4 (0.04)	1 (0.05)	4 (0.08)
Renal (n,%)	16 (0.08)	6 (0.06)	1 (0.05)	10 (0.2)
Sarcoma (n,%)	5 (0.02)	1 (0.01)	0 (0)	1 (0.02)
Stomach (n,%)	7 (0.03)	4 (0.04)	0 (0)	2 (0.04)
Testicular (male) (n,%)	1(0.01)	0 (0)	0 (0)	0 (0)
Bladder (n,%)	20 (0.10)	3 (0.03)	3 (0.14)	8 (0.16)
Prostate (male) (n,%)	32 (0.16)	10 (0.09)	2 (0.09)	62 (1.24)

AC- Anticoagulant; BOTH- Anticoagulants and SCD; LOS=Length of stay; NONE- no anticoagulant; SCD- Sequential Compression Device; SD=Standard deviation. Obesity defined as BMI >30 kg/m^2. Missing data: LOS=12, Gender=1.

Table 2: Effect of sequential compression device on incidence of venous thromboembolism compared to no prophylaxis

Model	Odds ratio	95% confidence interval	p-value	Covariates
Unadjusted	1.27	0.75-2.14	0.37	NONE
Adjusted for covariates	0.99	0.57-1.74	0.98	Log(age), spline CCI, spline Log(LOS), infection, pulmonary disease
Propensity matched	0.90	0.48-1.70	0.75	Non-parsimonious propensity score model for SCD receipt. See text

CCI=Charlson Comorbidity Index; LOS=length of stay; SCD=Sequential Compression Devices;