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Low-dose Vitamin K Can Improve Warfarin Control in Patients on LVAD Support

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Abstract

Background

Anticoagulation with oral vitamin K antagonists (VKA) is very important in patients supported on a left ventricular assist device (LVAD) to prevent thromboembolic complications. Some patients tolerate VKAs poorly and have an unstable INR as a result. It is reported that low-dose vitamin K can improve INR control in patients with an unstable INR in other clinical settings. We evaluated its safety and effectiveness in patients on LVAD support.

Methods

The records of all patients supported on an implantable LVAD between January, 2013 and March, 2014 were reviewed retrospectively to identify those who had received low-dose vitamin K while on warfarin. INR values and warfarin doses before and after initiation of vitamin K supplementation were compared to evaluate its effectiveness.

Results

There were six LVAD patients who were on low-dose vitamin K due to an unstable INR out of a total of 59 VAD patients followed as an outpatient. The standard deviation (SD) of INR decreased significantly after starting vitamin K ($p=0.04$) while the SD of warfarin dose did not ($p=0.22$). Comparing divergence from target INR, INR became significantly closer to target INR after starting vitamin K. The number of bleeding complications tended to be fewer on vitamin K, but this did not reach statistical significance ($p=0.09$).

Conclusions

Daily low-dose vitamin K supplementation can improve INR control in LVAD patients with unstable INR without increasing thromboembolic complications.

Keywords

Ventricular assist device; Vitamin K; Warfarin; LVAD; INR

Introduction

Appropriate anticoagulation is important in the management of patients on left ventricular assisting device (LVAD) support.[1] A stable level of anticoagulation is desired to minimize anticoagulation-related morbidity.[2, 3] However, the degree of anticoagulation produced by vitamin K antagonists, such as warfarin, depends on various factors.[4] Maintaining an appropriate international normalization ratio (INR) often requires frequent blood tests and changes in the warfarin dosage. One cause of INR instability is insufficient daily vitamin K intake.[5] There are several reports of achieving a stable INR by adding low-dose vitamin K in patients with an unstable INR in those who have atrial fibrillation or other common needs for anticoagulation. [5] However, data on low-dose vitamin K in LVAD patients are lacking. Therefore, we evaluated the effectiveness of low-dose vitamin K to achieve stability in LVAD patients with an unstable INR.

Methods

The records for all patients on long-term support with a continuous flow LVAD and followed at Thomas Jefferson University Hospital between January 1, 2013 and March 31, 2014 were reviewed to identify those patients who were being treated with low-dose oral vitamin K due to an unstable INR. There were no specific criteria for the definition of an unstable INR. Vitamin K initiation was at the discretion of the treating physicians. Vitamin K tablets (100 mcg) were obtained by the patients as a dietary supplement at retail stores. Data on the INR and warfarin dosing were collected up to three months before and after initiation of vitamin K supplementation, reviewing patient charts retrospectively. When vitamin K was started during the implant hospital admission, data during the admission were used in addition to outpatient data to complete the three-month follow-up. When vitamin K was started during outpatient follow up, outpatient data were used. In order to compare the degree of INR control before and after initiation of vitamin K supplementation, three factors were evaluated statistically. Firstly, the variance of INR and warfarin doses was compared using F-test, since significantly smaller variance would suggest better control. Secondly, differences between measured INR and median of target INR range (divergence) were compared using Student's t-test. Smaller divergence indicates INR closer to target, proving better INR control. Lastly, average INR and warfarin doses were also compared to evaluate impact of vitamin K on actual INR values and warfarin dosage. The INR goal range was individualized for each patient and was based on clinical risk factors for thrombosis or hemorrhage, as well as prior thrombotic

or bleeding events. Complications from anticoagulation including bleeding and thromboembolic event were also evaluated.

Results

There were six LVAD patients who were on low-dose vitamin K due to an unstable INR out of a total of 59 VAD patients followed as an outpatient. In general, the patients had a labile INR, with values well above the therapeutic range on minimal warfarin, or fluctuating between supra-therapeutic and sub-therapeutic despite changes in warfarin dosing. Table 1 shows INR and warfarin doses of each patient before and after the initiation of vitamin K. The variance of INR was significantly smaller in five of six cases (83%) after initiation of vitamin K. The average INR decreased significantly in two of six cases (33%).

Differences between measured INR and median of target INR range (divergence) were significantly better in three of six cases (50%) after initiation of vitamin K. The average warfarin dose decreased significantly in one case but was not significantly different in other cases. In three of the patients, the average INR was below the lower end of the individualized target range after initiation of vitamin K, but the range of INR values obtained were narrower, corresponding to the improved divergence seen.

Table 2 shows averages of six patients and comparison of each before and after initiation of vitamin K. Average number of complications during follow up periods is also shown. The SD of INR decreased significantly after initiation of vitamin K ($p=0.04$) while the SD of warfarin doses did not ($p=0.22$). Comparing divergence of unstable patients before and after vitamin K, INR became significantly closer to target INR after initiation of vitamin K. None of the patients had thromboembolic complications after being started on vitamin K, even though INR tended to be lower. The number of bleeding complications tended to be fewer on vitamin K, but this was not statistically significant ($p=0.09$).

Table 1: Changes in warfarin control before and after initiation of vitamin K supplementation.

Case		No vitamin K	Vitamin K	Variance (F-test)	Difference (t-test)
1	INR (target 1.8-2.0)	2.41±1.23 (1.2-5.3)	2.94±1.34 (1.2-4.8)	NS	NS
	Warfarin (mg)	3.61±0.91	3.54±1.69	<0.05	NS
	divergence	0.88±1.00	1.23±1.16		NS
2	INR (target 1.8-2.0)	1.81±067 (1.1-3.5)	1.55±0.20 (1.3-1.8)	<0.001	NS
	Warfarin (mg)	5.58±1.36	3.84±1.32	NS	<0.01
	divergence	0.57±0.33	0.35±0.20		<0.05
3	INR (target 1.8-2.5)	2.54±0.80 (1.7-3.88)	1.92±0.43 (1.5-2.91)	<0.05	<0.05
	Warfarin (mg)	1.06±0.40	1.15±0.32	NS	NS
	divergence	0.63±0.63	0.44±0.21		NS
4	INR (target 1.5-1.8)	3.30±0.93 (1.3-4.36)	1.73±0.29 (1.3-2.57)	<0.001	<0.01
	Warfarin (mg)	3.56±2.25	4.56±0.37	<0.001	NS
	divergence	1.50±0.80	0.22±0.20		<0.01
5	INR (target 2.0-2.5)	2.27±1.18 (1.13-5.09)	1.74±0.50 (1.32-2.87)	<0.05	NS
	Warfarin (mg)	1.65±1.32	2.00±0.47	<0.01	NS
	divergence	0.98±0.67	0.57±0.19		<0.05
6	INR (target 2.0-2.2)	2.14±1.22 (1.28-3.61)	1.91±0.54 (1.43-3.44)	<0.001	NS
	Warfarin (mg)	0.94±1.04	0.81±0.40	<0.001	NS
	divergence	0.94±0.77	0.49±0.30		NS

Continuous data are expressed as mean ± standard deviation. Target range and highest and lowest values are shown for INR. Divergence is the difference between measured INR and median of target INR.

Table 2. Comparison of averages of 6 patients before and after initiation of vitamin K supplementation.

		No vitamin K	Vitamin K	p
INR	Mean	2.41±0.46	1.96±0.45	NS
	SD	1.00±0.22	0.55±0.37	<0.05
	divergence	0.86±0.78	0.56±0.63	<0.01
Warfarin (mg)	Mean	2.73±1.67	2.65±1.41	NS
	SD	1.21±0.56	0.76±0.54	NS
Bleeding		0.83±0.69	0.17±0.37	0.09
Thromboembolic		0	0	-

Continuous data are expressed as mean ± standard deviation. Data of bleeding and thromboembolic complications are number of events during follow-up periods.

Discussion

These results all indicate significantly better INR control after initiation of vitamin K supplementation, which can theoretically lead to fewer complications from INR out of therapeutic range. Furthermore, the absence of thromboembolic complication after starting low-dose vitamin K suggests safety of its use even in patients on an LVAD. The target range for INR in our patients has fluctuated with time as more data on the risk of pump thrombosis have become available. In addition, our target range varies between patients based on clinical criteria. Patients who have had numerous bleeding episodes will usually be assigned a low INR range, while a higher range will be used in those with heparin induced thrombocytopenia, atrial fibrillation, documented or suspected hypercoagulable state, or thromboembolic episodes. Despite the fact that half of our patients had an average INR below the lower limit of their target range, there was less divergence between their actual INR and target INR after initiation of vitamin K supplementation, suggesting better overall control. In addition, there were no thromboembolic events in any patients during the three-month follow-up period or since thereafter. Another advantage is that low-dose vitamin K therapy is

affordable and available over-the-counter, hence it can even be cost-beneficial by reducing complications and frequency of INR tests. The major limitations of this study are its retrospective design and relatively small number of cases. A prospective randomized case-control study with a larger case volume would be necessary to further validate the effectiveness of vitamin K in patients on LVAD support.

In conclusion, daily low-dose vitamin K supplementations potentially improve INR control in LVAD patients with unstable INR without increasing the thromboembolic complications.

Disclosure statement

The authors have no conflicts of interest to disclose.

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