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ORIGINAL ARTICLE

Long-Term Anticoagulation in Kawasaki Disease: Initial Use of Low Molecular Weight Heparin is a Viable Option for Patients with Severe Coronary Artery Abnormalities

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Abstract Patients with severe coronary artery involvement after Kawasaki disease (KD) require long-term systemic anticoagulation. We sought to compare our experience with thrombotic coronary artery occlusions, safety profile, and degree of coronary artery aneurysm regression in KD patients treated with low molecular weight heparin (LMWH) versus warfarin. Medical records of all KD patients diagnosed between January 1990 and April 2007 were reviewed. Of 1374 KD patients, 38 (3%) received systemic anticoagulation, 25 patients received LMWH from diagnosis onward, 12 of whom were subsequently switched to warfarin, and 13 received warfarin from onset. The frequency of thrombotic coronary artery occlusions was similar between drugs. Severe bleeding was more frequent in patients on warfarin, but minor bleeding was more frequent for patients on LMWH. Patients on warfarin were at greater risk of under-anticoagulation or overanticoagulation (defined as achieving an anti-activated factor X level or an international normalized ratio below or above target level) than patients on LMWH ($P < 0.05$). Maximum coronary artery aneurysm z-scores diminished with time for patients on LMWH ($P = 0.03$) but not for those on warfarin ($P = 0.55$). This study suggests that LMWH is a potentially viable alternative for patients, especially young ones, with severe coronary artery involvement after KD.

Keywords Anticoagulants · Coronary disease · Kawasaki disease · Pediatric · Thrombosis

Introduction

The development of coronary artery aneurysms is one of the most detrimental sequelae of Kawasaki disease (KD) [27]. Patients with multiple or large coronary artery aneurysms secondary to KD are at increased risk of developing coronary artery stenosis [20, 38], thrombosis [15], and, eventually, coronary artery occlusions, which could potentially lead to life-threatening myocardial infarcts [13, 18, 24, 25]. For such patients, although oral warfarin with long-term aspirin therapy is currently recommended, the use of subcutaneous low molecular–weight heparin (LMWH) along with aspirin has been suggested as an alternative [23, 43].

Pharmacokinetics of LMWH are known to be more predictable than those of warfarin, and quick achievement of adequate therapeutic level of anticoagulation is easier with LMWH, especially in younger children [9]. Furthermore, many problems and adverse events have been reported with the use of long-term oral anticoagulation therapy, including the need for frequent monitoring, bleeding complications, negative drug–diet and drug–drug interactions, as well as individual dosing difficulties [2, 32]. Previous studies have also shown that the choice of anticoagulation therapy could

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promote coronary artery remodeling and coronary artery aneurysm regression [10]. Maximal regression of coronary artery aneurysms occurs within the first year after acute-phase KD, and regression is rarely seen beyond that point [18]. We sought to compare our experience with the use of LMWH (Enoxaparin, Sanofi Aventis, Laval, Quebec, Canada) and warfarin in terms of preventing thrombotic coronary artery occlusion, safety profile, and degree of coronary artery aneurysm regression for patients with coronary artery aneurysms after KD.

Methods

Medical records of all patients with KD seen at The Hospital for Sick Children, Toronto, between January 1990 and April 2007 were reviewed. The study was approved by the Hospital's Research Ethics Board, and requirement for individual consent was waived for this retrospective study. Patients receiving systemic anticoagulation therapy at any point during follow-up were identified and investigated further.

Demographic information and relevant clinical history for each patient were collected. Data pertaining to the acute phase of KD, including clinical presentation, laboratory findings, treatment, and coronary artery outcomes, were abstracted. Complete presentation of KD was defined as presenting with at least 4 of 5 KD clinical features in addition to fever for at least 5 days [27]. All intravenous immunoglobulin (IVIG) treatment consisted of 2 g/kg IVIG given in a single infusion.

Anticoagulation Protocol

At The Hospital for Sick Children, systemic anticoagulation is indicated for all patients with large or giant coronary artery aneurysm(s). In earlier years, older children were often treated with long-term warfarin from the time of diagnosis onward, whereas younger children were treated with LMWH. In later years, because of our standard clinical protocol, almost all patients were started on LMWH and were switched to warfarin 12 to 18 months after the acute phase if clinically stable and free from thrombosis.

Information related to anticoagulation was collected. This included the type of medication received, duration of treatment, dosage, number of episodes of thrombosis, and bleeding complications. The anticoagulant treatment guidelines used for both LMWH and warfarin in these patients were developed at The Hospital for Sick Children and have been published elsewhere [22]. The guidelines are in accordance with the Eighth American College of Chest Physicians' recommendations for children diagnosed with KD [23]. In addition to systemic anticoagulation, the subjects also received antiplatelet agents (i.e., low-dose aspirin therapy [3 to 5 mg/kg/d]) [23]. Hematuria and intracranial, intraocular, retroperitoneal and/or gastrointestinal bleeds, as well as any bleeds requiring a transfusion, were classified as major bleeding events, whereas nuisance bleeding, such as bruising, gingival bleeding, and nose bleeds, were classified as minor bleeding complications.

Echocardiography Protocol

All available echocardiograms reports from time of diagnosis to last follow-up were reviewed for each patient. Echocardiograms for KD patients were performed based on a standardized protocol, which included measurement of the internal lumen diameter of all coronary arteries and detailed description of all coronary artery aneurysms. Echocardiograms for patients with severe coronary artery disease were performed at least every 2 weeks during the acute phase and until 6 weeks after recovery, then every 3 months for the first year and biannually thereafter. Coronary artery aneurysms dimensions were converted to z-scores based on body surface area, such that changes in coronary artery aneurysms size with time could be characterized without being affected by increasing age and body size [7, 16]. Maximum coronary artery aneurysm z-score was taken as the highest coronary artery aneurysms z-score of the right main coronary artery, the left main coronary artery, or the left anterior descending coronary artery. Coronary artery aneurysms were classified as small, large, or giant based on body surface area–adjusted z-score criteria [19].

Statistical Analysis

Trends in coronary artery aneurysm z-scores were modeled using maximum likelihood estimates obtained from linear regression models with an autoregressive covariance structure to adjust for multiple measurements per patient. The longitudinal regression models included all data points for all patients starting during the acute phase regardless of medication. The models adjusted for the fact that some patients received different medications at different points during their clinical course. Thus, these models take into consideration the timing of medication use from the acute phase in addition to trends occurring with time.

Exponential transformations were applied to coronary artery aneurysm z-scores to account for the skewed distribution of measurements. All branches and maximum coronary artery aneurysm z-scores were modeled separately. Models were further adjusted for initial coronary artery aneurysm z-scores, patient age at diagnosis, calendar year, and duration of treatment. Trends in coronary artery aneurysm z-scores with time were modeled separately for

patients on LMWH and warfarin. Because the potential for coronary artery aneurysm regression is known to be the highest in the first year after the acute phase [13, 36], coronary artery aneurysm regression in the year after the acute phase for patients who received consistent treatment (either LMWH or warfarin) during this period was compared. In a subanalysis, regression models were further restricted to patients treated with both IVIG and aspirin within 12 days of fever onset and who did not suffer a myocardial infarction during the acute phase. Frequency of bleeding episodes (by severity of episode) was calculated by dividing the total number of episodes by the number of patient-years of follow-up. All analyses were performed (C. M. and B. W. M) using SAS Statistical Software version 9.1 (SAS, Cary, NC).

Results

Patient Population and Follow-Up

A total of 1374 patients with KD were seen at The Hospital for Sick Children during the study inclusion period. Of those, 38 patients (30 male [79%]) were identified as having coronary artery aneurysm(s) and received systemic anticoagulation. Patients were followed-up for a median of 5 years ($\leq$16 years) and had a median of 8 echocardiograms ($\leq$20). A total of 339 echocardiograms representing 219 patient-years of follow-up (143 patient-years while on systemic anticoagulation) were reviewed.

Clinical Characteristics and Coronary Involvement

Complete clinical characteristics, including symptoms at presentation, laboratory findings, and treatment, are listed in Table 1. Patients were diagnosed with KD at a median age of 2.1 years (range 0.3–14.3). The majority of patients had complete presentation of KD, whereas only 11 patients (30%) had incomplete presentation. Treatment included aspirin in 37 (97%) patients and IVIG in 32 (84%) patients. Overall, many of these patients had a challenging acute phase: 13 (34%) patients received multiple IVIG infusions, and 16 (42%) patients received steroids. Median duration of hospital stay was 10 days (range 3–76). The right coronary artery was involved in 25 (66%), the left main coronary artery in 20 (53%), the left anterior descending artery in 22 (58%), and the circumflex artery in 10 (26%) patients. Complete details of cardiac complications and coronary artery aneurysms are listed in Table 1. The only statistically significance differences between the groups was a higher C-reactive protein (CRP) in the warfarin-only patients and a higher rate of circumflex artery involvement in those who received the warfarin–LMWH combination. All other patient characteristics were comparable between the study groups.

Anticoagulation Therapy

Of the 38 patients included, 25 received LMWH from diagnosis onward, 12 of whom subsequently received warfarin, and 13 patients received warfarin only. We found no differences in clinical characteristics or severity of coronary artery aneurysms between patients who received LMWH and those who received warfarin, indicating a lack of bias in treatment assignment. Patients received LMWH for a median of 1.0 year (up to 6.0 years) for a total of 31 patient-years and warfarin for a median of 4.8 years (up to 12.8 years) for a total of 112 patient-years.

Thrombosis

During the acute phase, before the start of any anticoagulation therapy, 6 (16%) patients developed one or multiple coronary artery thrombi, three of whom received treatment with antithrombotic or thrombolytic medication. A further 6 (16%) instances of thrombosis were observed, two of which occurred while patients were on LMWH, two while patients were on long-term warfarin, and the remaining two while switching from LMWH to warfarin. Before the start of anticoagulation therapy, 3 (8%) patients had myocardial infarctions; two of these patients were treated with abciximab, and all patients eventually recovered. There were no myocardial infarctions or deaths in patients while on anticoagulants.

Treatment Monitoring

While patients were on anticoagulation therapy, anticoagulation levels were monitored according to standard protocols [22]. Patients on LMWH were monitored daily until an anti-activated factor X (anti-Xa) level within target range was documented, and then monitored every 4 to 6 weeks. Doses were adjusted to maintain an anti-Xa level of 0.5 to 1.0 U/ml. Patients on warfarin were initially monitored approximately twice a week until reaching a stable international normalized ratio (INR) level, and then monitored every 4–6 weeks. Doses were adjusted to maintain an INR of 2.0–3.0. Patients on LMWH were found to be at lower risk of underanticoagulation or overanticoagulation (defined as achieving an anti-Xa level or INR below or above target level) than those on warfarin. In the year after the acute phase of KD, there were 21 instances of out of range levels (19 below and 2 above target anti-Xa) in 75 LMWH-monitoring instances (28%), while there were 42 out of range levels (33 below and 9 above target INR) in 81 warfarin-monitoring instances

Table 1 Patients characteristics by treatment group ($n = 38$)[a]

Patient characteristics	Warfarin only ($n = 13$)		LMWH and warfarin ($n = 12$)		LMWH only ($n = 13$)		P[b]
Clinical characteristics							
Male sex (%)	[13]	10 (77)	[12]	9 (75)	[13]	11 (85)	0.82
Median age at diagnosis (y)	[13]	3.6 (1.6–7.4)	[12]	4.0 (0.4–6.8)	[13]	1.3 (0.5–3.0)	0.67
Median days of fever before diagnosis	[10]	10.7 ± 6.9	[10]	11.4 ± 7.4	[11]	11.3 ± 6.4	0.97
Median total duration of fever (d)	[11]	20.5 ± 10.7	[11]	15.0 ± 6.1	[12]	13.8 ± 5.6	0.11
Median duration of hospitalization (d)	[9]	16 (8–34)	[10]	7 (5–11)	[12]	17 (9–30)	0.08
Symptoms (%)							
Conjunctivitis	[11]	10 (91)	[12]	9 (75)	[12]	12 (100)	0.15
Cervical lymphadenopathy	[11]	7 (64)	[12]	7 (58)	[12]	5 (42)	0.54
Oral mucosa changes	[11]	9 (82)	[12]	11 (92)	[12]	9 (75)	0.56
Polymorphous exanthema	[11]	10 (91)	[12]	10 (83)	[12]	11 (92)	0.78
Extremity changes	[11]	9 (82)	[12]	9 (75)	[12]	7 (58)	0.44
Incomplete presentation[c]	[13]	2 (15)	[12]	4 (33)	[13]	5 (38)	0.40
Laboratory investigations at diagnosis							
Median albumin (g/dL)	[6]	29 (25–31)	[9]	31 (27–35)	[8]	29 (24–34)	0.91
Median ALT (U/L)	[4]	26 (14–91)	[9]	20 (12–28)	[9]	36 (12–41)	0.97
Median AST (U/L)	[3]	28 (24–37)	[7]	44 (37–53)	[8]	32 (18–71)	0.69
Median CRP (mg/dL)	[3]	61 (43–141)	[8]	30 (23–45)	[7]	27 (22–32)	0.02
Median ESR (mm/h)	[7]	72 (26–100)	[9]	97 (91–104)	[10]	86 (62–110)	0.35
Median hematocrit (/cm^3)	[7]	0.32 (0.28–0.40)	[10]	0.30 (0.28–0.32)	[10]	0.26 (0.23–0.29)	0.07
Median hemoglobin (/cm^3)	[8]	104 (97–134)	[10]	103 (92–107)	[11]	89 (80–102)	0.05
Median platelet (/cm^3)	[8]	428 (363–755)	[10]	511 (335–685)	[11]	539 (434–865)	0.91
Median red blood cells (/cm^3)	[3]	4.4 (3.3–4.5)	[8]	3.7 (3.3–4.1)	[6]	3.4 (3.0–4.7)	0.66
Median white blood cells (/cm^3)	[8]	15.8 (10.8–21.0)	[9]	12.3 (9.4–20.4)	[11]	15.1 (9.7–18.2)	0.90
Treatment (%)							
Aspirin	[13]	12 (92)	[12]	12 (100)	[13]	13 (100)	0.38
Intravenous immunoglobulin	[13]	11 (85)	[12]	10 (83)	[13]	11 (85)	1.00
Standard treatment[d]	[13]	7 (54)	[12]	8 (67)	[13]	6 (46)	0.58
Multiple intravenous immunoglobulin	[13]	6 (46)	[12]	2 (17)	[13]	5 (39)	0.28
Steroids	[13]	4 (31)	[12]	6 (50)	[13]	6 (46)	0.58
Cyclophosphamide	[13]	1 (8)	[12]	0 (0)	[13]	0 (0)	1.00
Naproxen	[13]	3 (23)	[12]	2 (17)	[13]	0 (0)	0.20
Abciximab	[13]	0 (0)	[12]	1 (8)	[13]	2 (15)	0.35
Aneurysm(s) location and size at diagnosis (%)							
Right coronary artery involvement	[13]	9 (69)	[12]	8 (67)	[13]	8 (62)	0.92
Right CAA size (mm)		0.65 (0.30–0.85)		0.61 (0.32–0.68)		0.50 (0.38–0.63)	0.72
Right CAA z-score		+12.3 (+1.3, +19.7)		+12.6 (+8.3, +27.3)		+8.0 (+3.7, +15.1)	0.95
Left main coronary artery involvement (%)	[13]	8 (62)	[12]	5 (42)	[13]	7 (54)	0.61

Table 1 continued

Patient characteristics	Warfarin only ($n = 13$)		LMWH and warfarin ($n = 12$)		LMWH only ($n = 13$)		P^b
Left main CAA size (mm)	0.55 (0.36–0.77)		0.33 (0.31–0.46)		0.41 (0.32–0.52)		0.24
Left main CAA z-score	+8.5 (+1.0, +12.3)		+3.5 (+1.2, +5.6)		+4.5 (+1.7, +6.8)		0.43
LAD coronary artery involvement	8 (62)	[13]	8 (67)	[12]	6 (46)	[13]	0.56
LAD CAA size (mm)	0.51 (0.27–0.88)		0.66 (0.31–0.70)		0.41 (0.26–0.73)		0.87
LAD CAA z-score	+12.6 (+4.1, +17.3)		+14.6 (+5.6, +20.1)		+14.0 (+1.6, +23.8)		0.78
Circumflex coronary artery involvement (%)	2 (15)	[13]	6 (50)	[12]	2 (15)	[13]	0.08
Circumflex CAA size (mm) ($n = 29$)	0.26 (0.19–0.50)		0.41 (0.20–0.60)		0.30 (0.18–0.37)		0.35
Maximum CAA z-score	+17.2 (+13.0, +19.7)		+16.6 (+8.3, +27.3)		+15.2 (+4.3, +24.9)		0.97
At least 1 giant CAA (≥10)	13/13 (100)		12/12 (100)		11/13 (85)		1.00

[a] Median with 25th and 75th percentile, mean with SD, or frequency as appropriate. Numbers in square brackets represent the number of observations

[b] Chi-square for catagorical variables and three-way analysis of variance for continuous variables

[c] Fever lasting > 5 days and with <4 of 5 classic Kawasaki disease symptoms

[d] Received intravenous immunoglobulin and aspirin within 12 days of symptoms onset

CAA coronary artery aneurysm, *LAD* left anterior descending, *ALT* alanine transaminase, *AST* aspartate transaminase, *ESR* erythrocyte sedimentation rate

(52%) ($P < 0.05$). A similar pattern was seen for monitoring instances beyond the first year of treatment. A total of only 5 out of range levels (3 below and 2 above) in 72 LMWH-monitoring instances were observed (7%), whereas 324 out of range levels (183 below and 141 above) were observed in 817 warfarin-monitoring instances (46%) ($P < 0.001$).

Safety

A total of 60 bleeding episodes were observed while patients were on systemic anticoagulation. Of those, 50 were considered minor episodes, and 10 were considered major episodes. Of 25 patients who ever received LMWH, 13 (52%) experienced at least 1 bleeding episode, whereas 20 (80%) of 25 patients on warfarin experienced at least 1 bleeding episode ($P = 0.07$). While on LMWH, 16 minor episodes (0.52 episodes/patient-year) and 1 major episode (0.03 episodes/patient-year) were observed, for a total of 0.55 episodes/patient-year. Patients on warfarin experienced 34 minor episodes (0.31 episodes/patient-year, $P < 0.001$ vs. LMWH) and 9 major episodes (0.08 episodes/patient-year, $P < 0.05$ vs. LMWH) for a total of 0.39 episodes/patient-year ($P = 0.01$ vs. LMWH).

Coronary artery aneurysms Regression

The rate of coronary artery aneurysms regression was greatest in the first year after the acute phase, and no changes in coronary artery aneurysms z-score with time were seen in subsequent years. In regression models adjusted for multiple measurements per patient, age at diagnosis, initial coronary artery aneurysm z-score, calendar year, and total duration of treatment, patients treated with LMWH experienced a significant regression of coronary artery aneurysm z-scores with time for the right coronary artery, the left anterior descending artery, and for maximum coronary artery aneurysm z-scores (Table 2). No change with time was found in coronary artery aneurysm z-score for any branch or for maximum coronary artery aneurysm z-scores for patients who received warfarin (Table 2). In direct comparison between patients consistently treated with LMWH ($n = 20$) or warfarin ($n = 11$) during the first year after the acute phase, the use of LMWH was found to be associated with a significantly greater decrease in left anterior descending coronary artery aneurysm z-score and maximum coronary artery aneurysm z-scores during that period of time. Similar, albeit non-significant, trends were observed for right coronary artery aneurysm and left main coronary artery aneurysm z-scores (Table 3). Results from the additional subanalyses (restricted cohort), as described in the statistical analysis section, yielded similar results as those reported.

Table 2 Coronary artery aneurysm z-score change with time

	PE (SE)	*P*
LMWH		
Right CAA z-score	–0.204 (0.106)	0.06
Left main CAA z-score	–0.128 (0.095)	0.18
Left main anterior descending CAA z-score	–0.363 (0.116)	0.002
Maximum CAA z-score	–0.292 (0.095)	0.003
Warfarin		
Right CAA z-score	0.012 (0.028)	0.66
Left main CAA z-score	0.008 (0.028)	0.77
Left main anterior descending CAA z-score	0.004 (0.035)	0.91
Maximum CAA z-score	0.016 (0.026)	0.55

CAA coronary artery aneurysms, *PE* parameter estimate, *SE* standard error

Regression models are adjusted for multiple measures per patients, age at diagnosis, calendar year, initial coronary artery aneurysm z-score, and duration of treatment

Reported is the change in coronary artery z-score per year of treatment in multivariable regression models (logarithmic transformation). Patients who received both LMWH and warfarin are included in both groups at different time points according to their treatment history

Table 3 Differences in coronary artery aneurysm z-score regression within 1 year of diagnosis between patients treated with LMWH only ($n = 20$) versus warfarin only ($n = 11$)

	EST (95% CI)	*P*
Right CAA z-score	–2.7 (–6.6 to 2.7)	0.30
Left main CAA z-score	–1.8 (–5.8 to 4.9)	0.54
Left anterior descending CAA z-score	–5.1 (–7.2 to –2.2)	0.003
Maximum CAA z-score	–4.7 (–7.4 to –1.3)	0.01

CAA coronary artery aneurysms, *EST* regression equation estimates, *CI* confidence interval

Regression models are adjusted for multiple measures per patients, age at diagnosis, calendar year, initial coronary artery aneurysm z-score, and duration of treatment

Discussion

This is the first study to report a large KD population treated with LMWH in the context of coronary artery aneurysms occurring after KD. We found that outcomes for LMWH are comparable with those with warfarin and that LMWH is a viable alternative to warfarin, especially in very young children and for the first year after acute-phase KD. The acute inflammatory process and accompanying structural changes affecting coronary arteries in KD lead to abnormal blood flow and shear forces, increased platelet activation, endothelial cell activation with expression of adhesion molecules and selectins [26], and further coronary artery wall damage. KD has long been recognized to be associated with coagulation-related changes in both the acute and nonacute phases of the disease regardless of coronary artery abnormalities [1, 6, 11, 28, 41].

Long-term anticoagulation therapy in patients with KD is aimed toward the prevention of intracoronary thrombus formation and the resulting myocardial ischemia and potential risk of sudden death. Current recommendations for systemic anticoagulation include the use of aspirin with warfarin [27]. The use of antiplatelet therapy alone without anticoagulation is not recommended for those patients because a previous study found that the use of antiplatelet therapy alone in KD was associated with a significantly higher incidence of myocardial infarction than a combination of antiplatelet therapy and warfarin [33]. Inherent problems associated with warfarin use in children, such as difficulties in predicting dose response and safety concerns, have led clinicians to explore alternative anticoagulation strategies. Recent studies have shown that vascular remodeling after acute-phase KD could be influenced by pharmacologic therapy, which emphasizes the importance of the choice of anticoagulant [42]. This study found that there could be some inherent advantages to the use of LMWH instead of warfarin regarding the promotion of vascular remodeling during the year after acute-phase KD without increasing the risk of thrombosis or bleeding.

Thrombosis Prevention

Previous studies have shown that a combination of prophylactic warfarin and aspirin was preferable for KD patients with giant coronary aneurysms in preventing the formation of obstructive lesions compared with no anticoagulation [29, 33, 37]. In this cohort, only 6 episodes of thrombosis were observed, 4 of which occurred when patients were being treated with warfarin. Our study findings suggest at least similar efficacy for both drugs in terms of thromboprophylaxis effect.

Monitoring and Safety

Warfarin requires frequent monitoring to ensure maintenance of a therapeutic INR; thus, it is difficult to dose (especially in younger children) and is associated with several drug–diet interactions [2, 12, 21, 32, 41]. Genetic polymorphisms are associated with varied response to warfarin in the initial stage and during maintenance therapy, which further increases complexity of management [31]. Failure to achieve an adequate anticoagulation target was found to be more frequent with warfarin than with LMWH, providing evidence concerning difficulties in management with the former drug.

During 143 patient-years of treatment, 10 severe bleeding episodes were recorded, whereas nuisance bruising and minor bleeding episodes were frequent and were

more prevalent with LMWH. The fact that the frequency of major bleeding episodes was higher in patients treated with warfarin might be a reflection of dosing difficulties as mentioned previously. Many monitoring instances for warfarin were above the target INR, which might suggest that some patients are overanticoagulated and thus are at higher risk of bleeding.

Furthermore, unlike LMWH, which is subcutaneously administered, drug–drug interactions with negative consequences are a setback for warfarin, which is an oral anticoagulant. In particular, it has been shown by Delaney et al. that the combination of aspirin and warfarin is associated with an increased risk of gastrointestinal haemorrhage compared with either drug alone [8]. Studies have also shown that long-term complications associated with the use of warfarin in pediatric patients have been linked to the development of osteoporosis. In comparison, LMWH has low affinity for plasma proteins, platelets and, osteoblasts, which results in a lower incidence of osteoporosis [3, 4, 23].

Vascular Remodeling

Although small coronary artery aneurysms have been shown to have the potential to regress in size with time, large lesions, such as those requiring long-term anticoagulation, are unlikely to show complete regression. In this perspective, promoting vascular remodeling, even in the absence of potential for normality, remains an important objective [34]. Although primarily used for its anticoagulant properties, heparin and its derivatives also possess anti-inflammatory activity. The potential anti-inflammatory effect of heparin is supported by several modestly sized trials in distinct scenarios in which inflammation was involved [5, 39]. The mechanisms responsible for this effect are not well understood, but they probably relate to the fact that heparin compounds can bind and neutralize a wide variety of mediators released from inflammatory cells, thus inhibiting their activity and further inflammation [10]. In addition to its modulatory effect of cellular apoptosis, an important component of vascular remodeling [17, 40], LMWH has also been shown to inhibit neutrophil adhesion to endothelial cells. The most prominent histopathologic feature of the coronary artery lesions in KD is thickening of the intima due to extracellular matrix production, smooth cell migration, and cell proliferation [35]. The affected areas express a variety of vascular growth factors, including transforming growth factor-β, platelet-derived growth factor, basic fibroblast growth factor, and vascular endothelial growth factor (VEGF) [35]. Heparin and LMWH have been shown to inhibit endothelial cell proliferation and organization effect in the presence of VEGF, especially LMWH fragments close to 6 kDa [14]. This study shows a potential association between LMWH and vascular remodeling and no association between vascular remodeling and warfarin treatment. Appropriate adjustments were made for factors known to be associated with greater rates of coronary artery aneurysm regression, such as initial coronary artery size, age at diagnosis, and total duration of treatment [30].

Limitations

This study should be considered in light of some potential limitations. This was a retrospective study on a small population that enrolled patients during a period of 17 years, during which there were multiple improvements in imaging techniques. In the context of long-term systemic anticoagulation after severe coronary artery complications, it still represents a large population that was regularly followed-up according to standard protocols. Furthermore, calendar years were included in all regression models, providing some adjustment for any potential improvements in imaging techniques. Treatment assignment was at the discretion of the responsible physician and was not subject to any form of randomization. Treatment duration was not standardized and many patients received both treatments at different times during their follow-up, thus introducing potential for confounding by indication. The use of multivariable models in which patient-specific characteristics thought to be potentially influencing regression, including patient age at diagnosis, initial coronary artery aneurysm size, and duration of treatment, allowed for some adjustment for the lack of randomization and for differences in treatment duration. There is no standard reporting of bleeding complications in this population, and as such our conclusions regarding bleeding episodes are limited to those complications noted in the medical records.

IVIG has become the standard treatment for KD. Approximately 5 to 6% of patients treated with IVIG within 12 days of illness and 15 to 20% of those not treated with IVIG within that time frame or not treated at all develop coronary artery aneurysms as a result of KD [30]. In our study population, 15% of patients never received IVIG, which might raise questions about the generalizability of the study to the current KD population. Currently, approximately 90% of patients presenting with KD are treated with aspirin and IVIG within 12 days of illness, which means that a substantial number of patients still do not receive appropriate treatment. A subanalysis of patients who developed coronary artery aneurysms despite timely IVIG-and-aspirin treatment found similar results. As such, the results from this study are applicable to both types of patients: those developing coronary artery aneurysms despite current clinical protocols as well as those who received IVIG too late, if at all.

Conclusion

In a relatively large KD patient population, we compared our experience with long-term systemic anticoagulation with warfarin or LMWH in addition to aspirin therapy. We found that the use of LMWH was associated with similar frequency of thrombosis, lower rates of underanticoagulation or overanticoagulation, and less frequency of major bleeding episodes but higher frequency of minor bleeding episodes. LMWH was found to be a potentially superior choice of anticoagulant than warfarin in terms of coronary artery aneurysm regression.

Results from this nonrandomized comparison should be considered in the context of the study limitations and validated in randomized clinical trials, and future research should focus on the use of novel anticoagulants and antiplatelet agents. This study suggests that LMWH is a potentially viable alternative for patients with severe coronary artery involvement occurring after KD, especially in younger patients and during the initial year after acute-phase KD.

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