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REVIEW

Parnaparin: A Review of its Safety and Efficacy

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Abstract

Introduction: Parnaparin, a low molecular weight heparin (LMWH), has a greater anti-thrombotic to anticoagulant activity ratio in comparison with unfractionated heparin (UFH). Moreover, its subcutaneous administration permits a greater bioavailability and a longer half-life than UFH, allowing a more practical once-daily dosage.

Objective: To evaluate the methodology and cumulative evidence presented in systematic reviews and in clinical trials about the safety and efficacy of parnaparin use in vascular disorders.

Materials and methods: Electronic literature sources were used to identify parnaparin trials and reviews published from 1984 to April 2010. The search was carried out in MEDLINE, EMBASE and PASCAL; search terms were "parnaparin" or "parnaparin sodium" or "fluxum". We identified various trials regarding parnaparin and its use in the prevention and treatment of venous disorders, in the treatment of acute coronary syndromes and peripheral arterial occlusive disease (PAOD), and we found a recent parnaparin trial in the treatment of retinal vein occlusion. We included two reviews regarding the clinical use of the drug.

Conclusion: Parnaparin has been shown to be safe and effective for the prevention and treatment of venous thromboembolism, for the treatment of acute coronary syndromes and PAOD.

Subcutaneous parnaparin is at least as effective as subcutaneous UFH in preventing deep venous thrombosis and pulmonary embolism. In the treatment of patients with acute coronary syndrome, subcutaneous parnaparin is associated with a lower incidence of a triple composite endpoint of death, acute MI or need for myocardial revascularization.

Long-term treatment with subcutaneous parnaparin in patients with PAOD significantly improves time and distance of pain-free walking compared with baseline. In the treatment of patients with retinal vein occlusion parnaparin seems to be more effective than aspirin in preventing functional worsening.**Parnaparin is a useful option in the range of LMWHs for the prevention and treatment of the several vascular disorders.**

Keywords: low molecular weight heparins, heparin, parnaparin, pharmacodynamics, pharmacokinetics, clinical use

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Introduction

For almost a half century unfractionated heparin (UFH) has been used in prevention of venous thromboembolism in the treatment of chronic venous disorders and as therapy of venous and arterial thrombosis. After 50 years heparin remains the most widely used parenteral antithrombotic drug.[1]

The general adoption of LMWHs represents a significant therapeutic advance in terms of safety and efficacy. LMWHs are manufactured from UFH by controlled depolymerisation using chemical or enzymatic methods.[2] LMWHs have represented a milestone in the prevention of DVT because of their greater antithrombotic to anticoagulant activity ratio in comparison with UFH, greater bioavailability and longer half-life than UFH, permitting a convenient once-daily administration.[3] Routine pharmacological prophylaxis and treatment with LMWHs is currently the standard practice to reduce the incidence of venous thromboembolism.

Parnaparin (Fluxum®) is a low-molecular-weight heparin (LMWH) that plays a significant role in the prevention and treatment of venous and arterial thrombosis.[4] As with other LMWHs, parnaparin has a predictable dose-response relationship, offers a high bioavailability at low doses and produces linear pharmacokinetics and a rapid antithrombotic action after administration.

This review focuses on the efficacy and the safety of parnaparin in the prevention and treatment of venous thromboembolism, in the treatment of chronic venous disease, coronary arterial disease and peripheral arterial occlusive disease.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Mechanism of action

Blood coagulation and the fibrinolytic process depends on a complex network of serine proteases, in which their activators and inhibitors exist in a delicate equilibrium to regulate steady blood flow and hemostasis. Alterations of this balance, due to a pharmacologic or pathophysiologic causes, can result in thrombotic or bleeding complications. A central role in this regulation is played by the serine protease thrombin, which is the target of most anticoagulant and antithrombotic drugs that also target other serine proteases such as factors XIIa, Xa and VIIa.[5]

UFH is a heterogeneous group of glycosaminoglycans synthesised in mast cells, consisting of a basic structure of alternating saccharide residues of uronic acid and glucosamine with a molecular weight ranging between 4 and 30 kDa. The saccharides are modified by a number of enzymes that chemically alter the molecular structure at specific sites, such as adding a sulfate or glucuronic acid moiety. The essential heparin core resides in short pentasaccharide fragments that interact with two endogenous proteins, antithrombin (AT III) and heparin cofactor II (HC-II), to mediate its anticoalgulant effect targeting various vascular and cellular sites.

Heparin interacts with AT III and HC-II and can produce differential inhibition of thrombin and its generation by factor Xa. This down regulation of thrombin function also impacts on the thrombin-thrombom odulin-mediated pathways, which directly affects the generation of activated protein C and the active form of TAFI (thrombin activatable fibrinolytic inhibitor).[5]

LMWHs are extracted from UFH of animal origin via enzymatic, chemical or physical processes. Because of their different fragmentation, the coagulation factors IIa and Xa are affected differently by AT III and therefore, the antithrombotic activity is separated by the anticoagulant effect depending on a larger anti-Xa activity compared with anti-IIa activity.

The biological properties of LMWHs are primarily determined by molecular weight, as shown in Table 1.

Parnaparin is the sodium salt of a low molecular weight heparin obtained with a patented fragmentation procedure by depolymerization of heparin from

Table 1. Different biological characteristics among LMWHs compared to UFH.[2,6]

Product	Depolymerisation	Mean MW (D)	Anti-Xa/ anti-IIa
Nadroparin calcium	Nitrous acid depolymer	4300	2.5–4.0
Enoxaparin sodium	Alkaline depolymer	4500	3.3–5.3
Parnaparin sodium	Radical catalysed oxidative depolymer	4500	>4
Dalteparin sodium	Nitrous acid depolymer	6000	1.9–3.2
Tinzaparin sodium	Controlled enzimatic depolymer	6500	1.5–2.5
Sodium UFH	–	15000	1

porcine intestinal mucosa. This original fragmentation guarantees the homogeneity of each fragment in term of molecular weight and length to optimize and maintain an anti-Xa/anti-IIa ratio of >4.[1] The anti-Xa/anti-IIa activity rate expresses the relationship between the doses producing the desired antithrombotic effects, and those producing the undesired anticoagulant activity.

Heparin and LMWHs inhibit functional TAFI. The inhibition, however, is not the same for all heparins, largely depending on the proportion of anti-IIa, as thrombin plays a major role in the activation of TAFI, as previously described. UFH has the strongest inhibitory effect of TAFI with a IC50 of 0,1, and all LMWHs have a lower effect than heparin on the TAFI pathway, as shown in Table 2.[5]

The IC50 values of the various heparins strongly correlate with anti-IIa activity but not with anti-Xa activity, suggesting that the inhibition of TAFI is not dependent on anti-Xa potency, as can be seen in Table 2.[5]

Thus, heparins mediate their therapeutic effect partly by inhibiting activated TAFI, which plays a significant role in the regulation of fibrinolysis.

Metabolism

Parnaparin is metabolized both in the liver and in the kidneys, whereas other LMWHs is cleared principally by the kidneys.[7] The effects of renal or hepatic impairment have not been reported, but it is known that the creatinine clearance is inversely correlated with LMWHs anti-Xa effect. To avoid accumulation of LMWHs the value of creatinine clearance has to be greater than 30 ml/min. In fact, renal insufficiency is associated with an increased risk of bleeding complications with therapeutic doses of LMWHs. Therefore, prophylactic doses of parnaparin may be safer in patients with severe renal insufficiency given the concurrent hepatic metabolism. However, if therapeutic doses are needed, low doses of weight-adjusted parnaparin or UFH, that is not cleared by the kidney, should be used.[8]

Table 2. IC50 values, anti-IIa and anti-Xa effect.[5]

Product	Anti Xa (IU/mg)	Anti Iia (IU/mg)	IC50
Enoxaparin sodium	100–110	23–28	1
Parnaparin sodium	85–90	25–30	0.8
Tinzaparin sodium	80–85	45	0.65
Dalteparin sodium	140–150	60	0.6
Sodium UFH	160–180	160–180	0.1

The neutralization of parnaparin by protamine chloride has been studied *in vitro* by coagulations tests such as APTT and anti-Xa activity. Parnaparin activity has been completely neutralized by protamine with a parnaparin/protamine ratio of IUaXa/20µg, whereas anti-Xa activity has been partially but substantially neutralized by protamine.[9]

Pharmacokinetic profile

Parnaparin, as previously mentioned, inhibits factor Xa (antithrombotic effect) more efficiently than factor IIa (anticoagulant effect), resulting in a greater anti-Xa/anti-IIa effect ratio than UFH. As with other LMWHs, assessments have been made indirectly *ex vivo* by measuring anti-Xa activity, which is considered the main antithrombotic mechanism.

Studies in healthy volunteers demonstrate that the inhibition of factor Xa occurs intensively and rapidly 2–4 hours after administration of parnaparin, is dose-dependent and persists for many hours after subcutaneous administration of a single bolus of parnaparin 3200, 6400 and 12800 IUaXa. Inhibition of factor Xa activity is maintained approximately 6 to 12 hours after administration of parnaparin 3200 or 6400 IUaXa, with demonstrable anti-Xa activity still occurring at 20 hours with the 6400 IUaXa dose.[10] Small, transient, dose-dependent inhibition of factor IIa is observed after administration of a single dose of subcutaneous parnaparin 3200, 6400 or 12800 IUaXa. However, anti-IIa activity is undetectable 4, 8 and 12 hours after the administration.[10]

The effect of subcutaneous parnaparin on aPTT is also small and dose dependent, with only the highest dose (12800 IUaXa) causing a peak value that reaches the lower limit of clinical significance.[2] Intravenous parnaparin 160 IUaXa/kg has a greater ratio of anti-Xa to anti-IIa activity than intravenous UFH 100 IU/kg and a shorter aPTT.[4]

In healthy volunteers the peak inhibition of factor Xa (Emax) after subcutaneous administration of parnaparin is dose-dependent (0.27 IU/mL after administration of 3200 IUaXa, 0.58 IU/mL with 6400 IUaXa). After intravenous administration Emax is approximately 5-fold greater than after subcutaneous administration of

Table 3. Different pharmacokinetic properties of LMWHs and UFH.[14,4,2]

Product	Bioavailability	Tmax (hours)	Half-life (hours)	Elimination	Protamine neutralization (%)
Nadroparin sodium	98%	4–6	8–10	Renal	57.7
Enoxaparin sodium	>90%	3	4.4	Renal	54.2
Parnaparin sodium	>90%	3	6	Renal	60.0
Dalteparin sodium	80%–90%	3–4	4	Renal	74.0
Tinzaparin sodium	90%	4–6	1.5	Renal	85.7
Sodium UFH	10%–30%	3	1	Saturable: binds to reticular-endothelium system, liver, spleen. Nonsaturable renal excretion.	100

the same dose (for example, mean Emax 1.35 IU/mL after iv administration of 3200 IUaXa).

As shown in Table 3, parnaparin is rapidly absorbed with a time to peak inhibition of factor Xa activity (Tmax) of 3 hours following subcutaneous administration and 5 minutes after intravenous administration, regardless of dose.[4] Independently of the site of subcutaneous injection, including abdominal, gluteal and deltoid regions, the bioavailability of the drug is almost 100%.[11] Steady state inhibition of factor Xa activity following subcutaneous parnaparin 3200 or 6400 IUaXa daily was achieved within 2–4 days.[12] No signs of drug accumulation after repeated once-daily subcutaneous administration for 7 days have been detected.[13]

Clinical Studies

Clinical evidence for the efficacy of subcutaneous parnaparin has been demonstrated in several studies regarding the prevention of venous thromboembolism disease, the management of chronic venous insufficiency and phlebopathies, coronary artery disease and peripheral arterial occlusive disease (PAOD).[7] We present a brief review of clinical studies in these different situations.

Prevention of venous thromboembolism

There are several clinical parallel-group non-randomized studies that compare parnaparin in its two dosages (3200 or 6400 IUaXa) with UFH 5000 IU administered subcutaneously two or three time daily[15–18] as prevention of venous thromboembolism (see Table 4). Prophylactic therapy is generally initiated 2 hours before a low- to medium- thromboembolic risk surgery and 12 hours before a high-thromboembolic risk surgery; the treatment lasts for 4 to 30 days, depending of the study.

There are also cohort studies,[19–22] randomized double-[23] or single-[24] blind trials and randomized nonblinded[25] studies because of the different administration regimens. In these trials patients undergo different types of surgery: general,[15,16,23,26–30] orthopedic,[17,18,20] cardiac,[25] urologic,[24,31,32] vascular,[21,33] gynaecologic[22] and bariatric[19] procedures. The endpoints were the frequency of deep venous thrombosis (investigated with venography, ultrasonography, fibrinogen uptake test or plethysmography) and of pulmonary embolism (PE, diagnosed with ventilation/perfusion lung scan or chest X-ray).

The largest of these trials was a multicentric study that included 610 patients divided into two equal groups undergoing general surgery and treated for 7 days to prevent a venous thromboembolic event.[15] The incidence of deep venous thrombosis (DVT) in the parnaparin group was significantly lower than in the UFH group. Also, the risk of bleeding seemed to be lower ($P = 0.032$) in the parnaparin group compared with UFH group.[15] The difference in the incidence of pulmonary embolism between the two treatment groups did not reach statistical significance.

Table 4. Important clinical trials using parnaparin for prevention of venous thromboembolism disease (see text).

Citacion (ref.)	Study type	Study population (surgery)	Parnaparin (IUaXa) sc	Comparator	Outcomes	Results parnaparin/ comparator rates (*P* value)
Verardi 1988[15]	PG	610 (major general surgery)	3200 or 6400 qd	UFH 5000 IU sc bid or tid	DVT PE bleeding	3.2/6.3 ($P < 0.05$) 0.32/1.0 NS 0.97/3.6 ($P = 0.032$)
Gruttadauria 1988[16]	PG	179 (general surgery)	3200 qd	UFH 5000 IU sc bid	DVT bleeding	2.2/4.4 ns 3.4/12.2 ($P = 0.048$)
Chiapuzzo 1988[17]	PG	140 (major orthopaedic surgery)	3200 qd	UFH 5000 IU sc tid	DVT PE bleeding	7.1/10.0 NS 0/0 4.2/7.1 NS
Mascali 1988[18]	PG	136 (major orthopaedic surgery)	3200 bid	UFH 5000 IU sc tid	DVT bleeding	1.5/2.4 NS 2.9/13.4 NS
Forestieri 2007[19]	C	10 (bariatric surgery)	6400 qd	–	DVT PE	0.0 1.0
Montebugnoli 2007[20]	C	509 (minor orthopaedic surgery)	3200 or 4250 qd	–	DVT PE bleeding	0.0 0.0 1.6
Gossetti 1992[21]	C	65 (major vascular surgery)	3200 qd	–	DVT bleeding	1.5 1.5
Tartaglia 1989[22]	C	92 (gynaecological surgery)	3200 or 6400 qd	–	DVT PE	3.3 0.0
Forzano 1989[23]	R, DB	100 (general surgery)	3200 qd	Placebo	DVT	2.0/12.0 NS
Corrado 1988[24]	R, SB	58 (urologic surgery)	6400 qd	UFH 5000 IU sc bid	DVT PE bleeding	0.0/0.0 0.0/0.0 0.0/0.0
Beghi 1993[25]	R, O	39 (cardiac surgery)	3200 qd	UFH 5000 IU sc tid	DVT	0.0/0.0
Garcea 1992[26]	R, O	90 (major general surgery)	3200 qd	UFH 5000 IU sc tid	DVT PE bleeding	0.0/2.2 NS 0.0/0.0 0.0/11.1 NS
Verardi 1989[27]	R, O	88 (major general surgery)	6400 qd	UFH 5000 IU sc bid	DVT bleeding	2.3/6.8 NS 0.0/0.0
Valle 1988[28]	R, DB	100 (general surgery)	3200 qd	Placebo	DVT bleeding	0.0/6.0 NS 2.0/6.0 NS
Catania 1988[29]	R, O	173 (general surgery)	3200 qd	UFH 5000 IU sc tid	DVT PE bleeding	1.1/7.1 ($P = 0.038$) 0/1.2 NS 0/0
Bonomo 1988[30]	C	78 (general surgery)	3200 qd	–	DVT bleeding	2.3 2.3
Pellegrino 1988[31]	C	87 (urologic surgery)	3200 or 6400 qd	–	DVT PE bleeding	2.3 0 2.3
Cortellini 1988[32]	C	80 (urologic surgery)	3200 or 6400 qd	–	DVT bleeding	6.2 5.0
Speziale 1988[33]	R, O	92 (vascular surgery)	6400 qd	UFH 5000 IU sc bid	DVT bleeding	6.5/8.6 NS 8.7/17.4 NS

Abbreviations: C, cohort study; DB, double blind; NS, not statistically significant; O, open; PG, parallel-group, nonrandomized; R, randomized; SB, single blind; qd, once daily; bid, twice daily; tid, three times daily.

Table 5. Important clinical trials using parnaparin for the treatment of venous thromboembolism (see text).

Citation (ref.)	Study type	Study population	Parnaparin (IUaXa) sc	Comparator	Outcomes	Results parnaparin/ comparator rates (*P* value)
Notarbartolo 1988[34]	R, O	90	6400 or 12800 qd	UFH 30000 IU iv qd or warfarin	DVT	0.0/0.0
					bleeding	0/3.1 ($P = 0.034$)
Teoldi 1993[35]	R, SB	40	6400 bid or 6400 qd	UFH 5000 IU sc tid or UFH 5000 IU sc bid	DVT	0.0/5.0 NS
					PE	0.0/0.0
					bleeding	0.0/0.0
Vashist 2006[36]	R, O	100	6400 qd + VKI	UFH 10000 IU sc tid + VKI	DVT	0.0/0.0
					PE	0.0/2.0 NS
					bleeding	0.0/0.0
Bellosta 2007[37]	R, O	91	6400 bid for 30 days, then 6400 qd	Nadroparin 11400 (<70 kg) or 15000 (>70 kg)	DVT	1.9/10.0 NS
					PE	1.9/0.0 NS
					bleeding	1.9/0.0 NS
Zinicola 1989[38]	C	47	12800 or 6400 qd	–	DVT	0
					PE	0

Abbreviations: C, cohort study; NS, not statistically significant; O, open; R, randomized; SB, single blind; qd, once daily; bid, twice daily; tid, three times daily.

In general, across all studies subcutaneous parnaparin is effective in the prevention of DVT and PE, but PE occurred too infrequently to allow a meaningful comparison of treatments. On the other hand, compared with subcutaneous UFH, parnaparin is at least as effective in preventing DVT.[29]

Treatment of venous thromboembolism

There are few randomized, single-centre studies comparing the efficacy of subcutaneous parnaparin with that of UFH[34–36] or nadroparin[37] in the treatment of DVT. In these trials subcutaneous parnaparin was administered once or twice daily at 6400 or 12,800 IUaXa and was compared with intravenous[34] or subcutaneous[35,36] UFH or with nadroparin.[37] In all studies parnaparin was at least as effective as the comparator in preventing recurrent extending DVT and PE with a similar safety profile, as shown in Table 5.

One study compared double daily administrations of parnaparin 6400 IUaXa for 1 month followed by parnaparin 6400 IUaXa/day for 2–5 months (depending on the thrombotic risk) with single daily doses of nadroparin 11400 IUaXa/day for bodyweights of <70 kg and 15,000 IUaXa/day for bodyweights >70 kg for 3–6 months.[38] The incidences of thromboembolic events were 3.9% in the parnaparin group versus 7.5% in the nadroparin group. The incidence of recanalization increased significantly in the parnaparin group: 45.1% achieving a resolution of thrombosis at 6 months versus 27.5% in the nadroparin group, and 60.8% versus 50.0%, respectively, achieving resolution at 12 months.[38]

Treatment of chronic venous disease

These clinical studies considered the treatment of a range of chronic venous diseases of the lower limbs, such as postphlebitic syndrome, thrombophlebitis, varicophlebitis and chronic venous insufficiency.

Four randomized trials[39–42] compared the efficacy of subcutaneous parnaparin with that of UFH. In three of these trials[40–42] parnaparin dosage was 4250 IUaXa once daily compared to UFH 5000 IU twice daily, and the duration of the treatment was 90 days. The degree of improvement in clinical and instrumental outcome was similar in both treatment groups, and because of their small sample sizes (n = 46 to 70) there was no statistically significant difference in terms of efficacy between parnaparin and UFH.

In a fourth study[39] patients (n = 77) commenced treatment with parnaparin 30000 IUaXa subcutaneously or UFH 20000 UI intravenously once daily for

Table 6. Important clinical trials using parnaparin for the treatment of chronic venous disease (see text).

Citation (ref.)	Study type	Study population	Parnaparin (IUaXa) sc	Comparator	Treatment duration (days)	Efficacy parnaparin/ comparator rates (*P* value)
Verardi 1988[39]	R, O	77	30000 qd for 10 days, then 15000 qd	UFH 20000 IU iv qd for 10 days, then UFH 12500 IU sc	50	7.0/8.0 NS
Catania 1993[40]	R, SB	46	4250 qd	UFH 5000 IU sc bid	90	NS
Canova 1993[41]	R, SB	57	4250 qd	UFH 5000 IU sc tid	90	NS
Della Marchina 1993[42]	R, SB	70	4250 qd	UFH 5000 IU sc tid	90	8.6/17.1 NS
Sannazzari 1989[43]	R, DB	92	3200 or 6400 qd	UFH 5000 IU sc tid	30	0.0; 0.0/6,7 ($P < 0.05$)

Abbreviations: NS, not statistically significant; O, open; R, randomized; SB, single blind; qd, once daily; bid, twice daily; tid, three times daily.

the first 10 days followed by parnaparin 15000 IUaXa or UFH 12500 IU subcutaneously for up to 50 days. In this study there was also no statistically significant difference in terms of efficacy.[39]

The only statistically significant trial[43] was a randomized double-blind study (n = 90) in which parnaparin 6400 IUaXa once daily was compared with UFH 5000 IU three times daily and 3200 IUaXa once daily. The duration of treatment was 30 days, and efficacy was measured by strain-gauge plethysmography (to analyze venous outflow) and clinical evaluation (spontaneous pain, ankle diameter). Efficacy was generally superior in the higher parnaparin dosage group than in the other two treatment groups (see Table 6).

Treatment of coronary artery disease

As shown in Table 7, a large, randomized, nonblind multicenter trial compared the efficacy of parnaparin with that of UFH in the treatment of unstable angina. Patients received subcutaneous parnaparin 6400 IUaXa once daily for one week or an initial intravenous bolus of UFH 5000 IU followed by intravenous infusion of UFH 800–1000 IU/hour for 48 hours, then subcutaneous UFH 5000 IU every 6 hours for 5 days. The results showed that parnaparin was statistically more efficacious than UFH as evidenced by the lower incidence of death, acute myocardial infarction and the need for myocardial revascularization in the first 7 days (primary endpoint) in the parnaparin group. Also, at the end of 30 days the incidence of these events was significantly lower in the parnaparin group. On the other hand, the incidence of recurrent angina in the two groups was the same.[44]

Another randomized, nonblind single-centre study considered patients with acute ST segment myocardial infarction (STEMI) treated either with parnaparin 4250 IUaXa for 7 days or a bolus of intravenous UFH 100 IU/kg, started 12 hours after thrombolysis, then continuous intravenous infusion of UFH 1000 IU/hour for 3 days followed by subcutaneous UFH 7500 IU twice daily for 4 days. The primary efficacy endpoint was a composite of death, acute myocardial infarction or emergency myocardical revascularization in the first 45 days following the start of the treatment. The statistical analysis between the two groups showed that parnaparin was more effective ($P = 0.03$) in treating patients with acute STEMI.[45]

Parnaparin was compared with placebo in a small (n = 29), randomized, double blind study of patients with stable angina who were not candidates for revascularization. In addition to aspirin and conventional antianginal therapy, the patients received subcutaneous parnaparin 6400 IUaXa once daily or placebo for 3 months. After the treatment period the parnaparin group was able to improve exercise time significantly on the treadmill compared with baseline, but there were no significant differences compared to placebo.[46]

Treatment of peripheral arterial occlusive disease (PAOD)

Several randomized trials compared parnaparin with placebo for the treatment of PAOD (see Table 8). Patients

Table 7. Important clinical trials using parnaparin for the treatment of coronary artery disease.

Citation (ref.)	Study type	Study population	Parnaparin (IUaXa) sc	Comparator	Treatment duration (days)	Efficacy parnaparin/ comparator rates (*P* value)
PRIME CARE 2005[44]	R, O	897	6400 qd	UFH bolus 5000 IU iv, followed by 800–1000 IU/h for 2 days, then 5000 IU qid sc for 5 days	7	7.3/11.4 ($P = 0.034$)
Wang 2006[45]	R, O	186	4250 bid	UFH bolus 100 IU/kg iv, then 100 IU/h for 3 days, then 7500 IU bid sc for 4 days	7	27.1/42.2 ($P = 0.03$)
Melandri 1993[46]	R, DB	29	6400 qd	placebo	90	NS

Abbreviations: NS, not statistically significant; O, open; R, randomized; DB, double blind; qd, once daily; bid, twice daily; qid, four times daily.

had stage II disease according to the Leriche-Fontaine classification and were treated with either subcutaneous parnaparin 6400 IUaXa once daily or placebo for 6 months.[47–52] In most of the studies significant improvement of pain-free walking time and distance from baseline was observed in patients treated with parnaparin compared to placebo. In addition, ankle-brachial index (ratio between ankle and brachial artery pressures) was significant increased at the end of the treatment period in the parnaparin group.[48]

In one nonrandomized, parallel group trial parnaparin (6400 IUaXa once daily) was compared with UFH (5000 IU twice daily); at the end of 7 months both groups had improved pain-free walking time and distance and ankle-brachial index, which was statistically evident in both groups after the first month of therapy.[53]

Treatment of retinal vein occlusion (RVO)

A recent multicenter, randomized, double blind, controlled study compared the efficacy and safety of aspirin (100 mg/daily for 3 months) versus parnaparin (12800 IUaXa for 7 days followed by 6400 IUaXa up to 3 months) in the treatment of RVO (see Table 9). The primary end-point of the study was the incidence of functional ophthalmologic deterioration with RVO at 6 months, as assessed by fluorescein angiography, visual acuity and visual field testing. Functional worsening was demonstrated in 20.7% of patients treated with parnaparin and in 59.4% of patients treated with aspirin ($P = 0.002$). Recurrent RVO, as a secondary outcome, was diagnosed in 3 patients, all treated with aspirin (NS), and bleeding rates were similar between the two groups. Parnaparin thus appeared to be more effective than aspirin in preventing functional worsening in patients with RVO, but due to the small sample size of patients (n = 58), the results should be confirmed in a larger clinical trial.[54]

Safety

Haemorrhagic complications are the most important side effects of LMWHs and UFH and can be divided in major bleeding (when haemoglobin loss is more than 2 g/L, requires transfusion of at least two units of packed red-blood cells or concerns life-threatening sites) and minor bleeding (such as at the injection site).[7]

Parnaparin used at a prophylactic dose (3200– 6400 IUaXa/day) does not present a significant risk of bleeding and is a lower risk when compared to UFH.[55] In fact, in the large trial mentioned previously in which patients underwent major surgery and received 7 days of prophylactic therapy, a clinically detectable haemorrhage occurred in 1% of patients receiving parnaparin versus 4% receiving UFH two or three times daily; a hematoma occurred at the injection site in 5% of parnaparin patients versus 23% of UFH patients.[15]

A study concerning the use of parnaparin in patients with unstable angina detected a significant difference ($P < 0.001$) regarding the incidence of minor bleeding between the parnaparin group (3%) versus UFH group (23%), although both groups reported one case of major bleeding.[44]

In a trial considering patients with STEMI, total bleeding events occurred in 3% of patients receiving subcutaneous parnaparin and 10% in patients

Table 8. Important clinical trials using parnaparin for the treatment of PAOD (see text).

Citation (ref.)	Study type	Study population	Parnaparin (IUaXa) sc	Comparator	Treatment duration (months)	Endpoint	Efficacy (*P* value)
Palmieri 1988[47]	R, DB	55	6400 qd	placebo	6	ABI, PFWD, SGP	NS
Tesi 1989[48]	R, DB	20	6400 qd $P = 0.03$	placebo	6	ABI PFWD	$P < 0.05$
Mannarino 1991[49]	R, DB	44	6400 qd $P < 0.05$	placebo	6	ABI PFWD	NS
Serrao 1991[50]	R, DB	40	6400 qd	placebo	6	CE, ABI, PFWD	$P < 0.05$
Simoni 1993[51]	R, O	66	6400 qd	placebo	6	DS, PFWD, TDM	$P < 0.05$
Calabrò 1993[52]	R, DB	36	6400 qd	placebo	6	ABI, PFWD, TDM	NS
Di Stefano 1988[53]	PG	55	6400 qd	UFH 5000 IU bid	7	CE, PFWD, TDM	NS

Abbreviations: ABI, ankle-brachial index; CE, clinical evaluation; DB, double blind; NS, not statistically significant; O, open; PG, parallel-group; PFWD, pain-free walking distance; R, randomized; SGP, strain-gauge plethysmography; TDM, treadmill; qd, once daily; bid, twice daily.

treated with intravenous and then subcutaneous UFH (NS).[45]

Because of severe haemorrhagic episodes described in one prevention study in surgical patients, treatment cessation was required in 5 of 45 patients treated with UFH but none of 45 patients receiving parnaparin.[26] In a study regarding patients undergoing major surgery there were no differences in the incidence of perioperative blood loss or transfusion requirements between patients receiving parnaparin 3200 IUaXa once daily or placebo for 7 days.[28] After minor orthopedic surgery bleeding complications were reported in <2% of patients treated with parnaparin, and most of them were hematomas at the injection site (minor bleeding).[20]

Caution should be used in patients with renal or hepatic insufficiency, arterial hypertension, or any organ lesion subject to bleeding.[56]

Heparin-induced thrombocytopenia (HIT) is another serious side effect following any exposure to UFH or LMWHs; it is defined as a decrease in platelet count of ≥50% with no other obvious explanation for thrombocytopenia and a positive test for heparin-dependent IgG antibodies. The frequency of HIT is thought to range from 1% to 5% of patients receiving UFH, three times more than patients receiving LMWH (0.8%).[57,58] This immune-mediated syndrome is paradoxically associated with thrombosis, not bleeding, with thrombin generation playing a central role. The diagnosis of HIT is based upon clinical findings that can be confirmed with laboratory assay; however, when there is clinical suspicion of HIT, all forms of heparin therapy should be immediately discontinued and initiation of alternative anticoagulation is strongly encouraged.

Table 9. Clinical trials using parnaparin for the treatment of retinal vein occlusion.

Citation (ref.)	Study type	Study population	Parnaparin (IUaXa) sc	Comparator	Treatment duration (months)	Endpoint	Efficacy parnaparin/ comparator rates (*P* value)
Ageno 2010[54]	R, DB	58	6400 bid for 7 days followed by 6400 qd	Aspirin 100 mg qd	3	Functional worsening	20.7/59.4 ($P = 0.002$)
						Recurrent RVO	NS

Although no current evidence suggests that parnaparin induces thrombocytopenia, and HIT was not observed in the clinical trials discussed in this review, patients receiving prophylactic or therapeutic parnaparin should be monitored with a platelet count during the first 10 days of treatment.

As other LMWHs, parnaparin does not cross the human placenta and is not detected in fetal blood during the first 6 months of pregnancy,[59,60] and thus it appears to be safe in pregnant women.[61,62]

Patient Preference

Parnaparin is well tolerated and has a general good patient acceptance, reported in all clinical studies in which it was investigated. As shown in Table 10 and similarly to other LMWHs, subcutaneous parnaparin has a better local tolerability than subcutaneous UFH, partly due to the lower frequency of administration. In fact, the tolerability of parnaparin at the local level seems better than that of UFH, given the lower incidence of hematomas, pain and burning in the injection site.[37,63] Furthermore, the convenient once-daily dosage schedule of parnaparin enables more patients to be treated at home or as outpatients than UFH, which improves their quality of life.[64] In addition, routine laboratory monitoring of parnaparin is less invasive than of UFH because parnaparin requires blood controls only during the first two weeks of treatment to avoid HIT and not as frequently as required to establish UFH dosages.[65]

A recent Italian trial comparing costs of LMWHs showed that parnaparin drug acquisition cost is the lowest among all LMWHs for the majority of their applications, permitting positive clinical and economical outcomes for patients, health system and society.[64]

Table 10. Advantages of parnaparin compared to UFH.

	Parnaparin	UFH
Dosing	once or twice daily	continuous infusion
Route	subcutaneous	intravenous
aPTT monitoring	no	yes
Dose adjustment	no	yes
Antithrombin effect	greater	–
Outpatient treatment	yes	no
Overall cost	Lower	–

Place in Therapy

Treatment guidelines generally recommend that LMWH should be used as a first-line drug for the treatment or prevention of DVT or PE based on its proven efficacy and on its pharmacokinetic advantages over UFH, as described in section 3.[61,65] The efficacy of parnaparin in several clinical trials is consistent with that of other agents of its class.

Parnaparin administrated subcutaneously (3200 UIaXa) once-daily for 7 days in patients undergoing major and minor surgery was shown to be more effective than placebo and at least as effective as UFH in preventing DVT or PE. Similarly, in the treatment of chronic venous insufficiency or phlebopathies parnaparin given once daily for up to 3 months was as effective as UFH.

In the management of acute coronary syndromes once daily parnaparin was associated with a significantly lower incidence than UFH of the triple composite endpoint of death, acute MI or need for myocardial revascularization in the first 7 days after the beginning of the treatment. In patients with stable angina a 3-month course of therapy with parnaparin provided a significant improvement in the exercise time on treadmill test compared with baseline.

In the treatment of PAOD, subcutaneous parnaparin administrated in patients with claudicatio intermittens (stage II of Leriche-Fontaine Classification) was compared with placebo and showed a significant improvement of pain-free walking time and distance, peak blood flow in the calf and in the ankle-brachial index.[7]

Conclusions

LMWH as a group has several advantages over UFH in terms of convenience of administration, efficacy and tolerability. Subcutaneous parnaparin is a LMWH that has been demonstrated to be safe and generally well tolerated in the prevention of venous thrombosis and in the treatment of chronic venous disease and in venous and arterial thrombosis. Overall, the efficacy of parnaparin is at least as good as that of UFH, but parnaparin was more effective in patients with unstable angina or acute STEMI in preventing death, acute MI and emergency myocardial revascularization.[7] Besides the clinical advantages, LMWHs including parnaparin have a greater bioavailability and a longer half-life than UFH that

allows simpler home management since they can be administrated subcutaneously once daily and do not require continuous lab tests.

The risk of general bleeding appears to be similar with parnaparin or UFH, although parnaparin results in fewer haematomas at the site of injection, partly because of less frequent administration regimen. Parnaparin has also been associated with a lower incidence of pain and burning sensation at the injection site compared with UFH.

No cases of HIT have been reported with parnaparin use; but the possibility of associated thrombocytopenia cannot be excluded, and a platelet count should be taken between the seventh and the tenth day of therapy.

Because of parnaparin is eliminated primarily by a nonsaturable renal mechanism, in patients with renal dysfunction parnaparin clearance may be reduced and anti-Xa activity should be carefully monitored.

In conclusion, few studies comparing LMWHs are available, and large studies would be needed because of the similarities between these drugs to detect important differences. In the mean time, the available data indicate that parnaparin is a useful option among all the commercially available LMWHs.[1]

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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