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Original Article

The effects of LMWH-Na on stopping the development of venous thrombus, on platelet-related indices, and on patients' coagulation functions after knee arthroplasty

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Abstract: Objective: This study aimed to analyze the effects of LMWH-Na on stopping the development of venous thrombus, on the platelet-related indices, and on patients' coagulation functions after knee arthroplasty. Methods: The clinical data of 85 patients undergoing knee arthroplasty in our hospital were retrospectively analyzed. According to the treatment modes, the patients were divided into a control group (CG), which received treatment with heparin sodium injections after knee arthroplasty, and an observation group (OG), which received treatment with LMWH-Na injections. The 2 groups were compared in terms of their clinical efficacy, coagulation function indices, including the formation and development of venous thrombus, D-dimer (DD), fibrinogen (FIB), their activated partial thromboplastin time (APTT), their prothrombin time (PT), their platelet related indices, including platelet distribution width (PDW), mean platelet volume (MPV), and platelet count (PLT), as well as the development of drug-related adverse reactions. Results: (1) In the OG, there were 18 patients who were considered cured, 15 patients whose treatment was considered markedly effective, 8 patients whose treatment was considered effective, and 2 patients whose treatment was considered ineffective, for a total effective rate of 95.35%, which was higher than the rate in the CG ($P<0.05$). (2) After the operation, the formation rate of venous thrombus was 2.33% in the OG and 21.43% in the CG ($P<0.05$); (3) The treatment also contributed to longer PT and APTT and shorter FIB and DD in the OG compared with the CG ($P<0.05$); (4) The OG reported higher PDW and MPV and lower PLT than the CG ($P<0.05$); (5) During the treatment, the incidences of adverse reactions, including pain at the injection site and gastrointestinal reactions, were 2.33% and 4.65% in the OG and 4.76% and 2.38% in the CG ($P>0.05$); furthermore, the OG reported a bleeding incidence of 0.00%, lower than the incidence of 19.05% in the CG ($P<0.05$). Conclusion: LMWH-Na is more effective at reducing the incidence of venous thrombus and improving the coagulation and platelet functions after knee arthroplasty and with higher drug safety.

Keywords: LMWH-Na injection, heparin sodium injection, knee arthroplasty, formation of venous thrombus, coagulation function

Introduction

Knee arthroplasty is commonly used to treat patients with knee problems at the terminal stage, in which the injured joints are replaced by artificial ones [1]. This operation not only corrects the force lines of the extremities, but it also alleviates the pain and effectively maintains joint stability [2, 3]. Until now, knee arthroplasty has been applied clinically for more than 20 years as an effective solution to tough problems in clinical orthopedics [4].

Regardless of its numerous advantages, such as improving joint structure, alleviating pain and correcting deformations [5], knee arthroplasty is sometimes followed by a serious major problem - the formation of venous thrombus [6]. To effectively prevent the formation of venous thrombus after knee arthroplasty, clinically, it is a general practice to enhance the drug treatment after the operation [7]. Heparin sodium injections are frequently used clinically to prevent and treat thrombosis diseases or thrombogenesis. In addition, the injections are also applicable in operations such as microvascular surgery, catheterization, extracorporeal circulation and hemodialysis [8]. Though the drug can yield ideal effects in terms of preventing and treating venous thrombus, it requires the measurement of the coagulation time during the medi-

cation, which restricts its clinical application further [9, 10]. LMWH-Na injections are mainly made of the sodium salts harvested from the glucosamine sulfate fragments after heparin sodium lysis and have demonstrated marketed effectiveness in inhibiting arterial and venous thrombus, thrombus in vitro, and in vivo [11].

Previous clinical studies of knee arthroplasty focused more on the surgical efficacy, and less on the postoperative formation of venous thrombus. This study innovatively compares the effectiveness of LMWH-Na injections and heparin sodium injections at eliminating the development of venous thrombus and compares their effects on platelet related indices and coagulation functions after knee arthroplasty.

Materials and methods

Materials

The clinical data of 85 patients undergoing knee arthroplasty in our hospital were retrospectively analyzed. According to the treatment modes, those patients were divided into the control group (CG, n=42, 22 males and 20 females) who received treatment with heparin sodium injections after knee arthroplasty, and the observation group (OG, n=43, 24 males and 19 females) who received treatment with LMWH-Na injections. (1) Inclusion criteria: patients who complied with the indications for joint replacement in *Orthopedic Surgery* [12] due to severe knee fracture on one side and who could tolerate the surgical treatment were included and provided their informed consent to participate in the study. The study was approved by the Medical Ethics Committee of the First People's Hospital of Wenling. (2) Exclusion criteria: some patients were excluded as they had coagulation dysfunction before the operation, severe organ function damage, venous thrombus, peripheral vascular diseases, malignant tumors, or a history of drug allergies or anticoagulant therapy, or because they withdrew from the study in the process.

Methods

After their knee arthroplasty operations, the patients in both groups used an intermittent charging and pressurizing device to prevent the formation of venous thrombus. Meanwhile, on the day the operation was performed, the patients in the CG were hypodermically injected with the heparin sodium injections (manufacturer: Tianjin Biochem Pharmaceutical Co., Ltd., approval document no.: GYZZ H12020505, specification: 2 ml:12,500 units) at a dose of 1.25×10^4 U qd, and the patients in the OG were hypodermically injected with LMWH-Na injections (approval document no.: GYZZ H10980115, manufacturer: Hangzhou Jiuyuan Gene Engineering Co., Ltd., specification: 2 ml:5000 IU) at a dose of 2500 U qd. The treatment continued for 1 week in both groups.

Observation indices

Criteria for the efficacy evaluation: if after one week of treatment, the patient yields a Lysholm score ≥90, and his/her knees can be hyperextended or extended without help, the patient is considered cured; if the Lysholm score is between 75 and 90, and the patient can extend his or her knees straight without help, the effects are defined as marked; if the Lysholm score falls between 60 and 75, and the knee joints can be extended with help but not without help, the effects are defined as effective; if the Lysholm score is under 60 and the knee activity is under 60°, the effects are defined as ineffective [13]. The total effective rate = effective rate + marketed effective rate + cure rate.

Formation of venous thrombus: the two groups were compared for the formation incidence of venous thrombus at 3 months after the operation. The judgment criteria of venous thrombus formation are as follows: extensive superficial venous engorgement, elevated skin temperature of the affected limbs and they appear dark red; extensive swelling; significant tenderness on the calves or the fossae scarpae major, and sharp pains in the affected limbs [14].

Coagulation function indices: before and after the treatment, 5 ml of blood was drawn from the patients' veins in the morning in a fasting state and then centrifuged at a speed of 3000 r/min to isolate the serum for future testing. DD was inspected using ELISA, FIB, APTT, and PT using an ACL TOP automatic coagulometer.

Platelet indices: PDW, MPV and PLT were measured before and after the treatment with an automatic globulimeter.

Table 1. Comparison of the OG and the CG in terms of the general data [n (%)]/($\bar{x}$ ± s)

Data		OG (n=43)	CG (n=42)	t/X^2	*P*
Gender (n)	M	24 (55.81)	22 (52.38)	0.101	0.751
	F	19 (44.19)	20 (47.62)		
Age (y)		42.58±1.25	42.56±1.23	0.074	0.941
Operation time (min)		68.96±3.15	69.06±3.13	0.147	0.884
Intraoperative amount of bleeding (ml)		97.02±2.58	97.01±2.53	0.018	0.986
Injured site					
Left knee		21 (48.84)	23 (54.76)	0.299	0.585
Right knee		22 (51.16)	19 (45.24)		

Table 2. Comparison of the OG and the CG in clinical efficacy [n (%)]

Group	n	Cured	Markedly effective	Effective	Ineffective	Total effective
CG	42	12 (28.57)	10 (23.81)	10 (23.81)	12 (28.57)	32 (76.19)
OG	43	18 (41.86)	15 (34.88)	8 (18.60)	2 (4.65)	41 (95.35)*
X^2						8.242
P						0.004

Note: *represents P<0.05 compared with the CG.

Adverse reactions: the two groups were compared in terms of their incidences of adverse reactions, such as pain at the injection site and gastrointestinal reactions during the treatment.

Statistical analysis

The statistical analysis was performed with SPSS 22.0. Numerical data were expressed as the mean ± standard deviation The comparison studies were carried out using independent-samples T tests for data which were normally distributed, and Mann-Whitney U tests for data which were not normally distributed and paired tests for pre-and-pro comparisons within a group; in the case of nominal data expressed as [n (%)], the comparison studies were carried out using X^2 tests for the intergroup comparisons. For all the statistical comparisons, significance was defined as P<0.05.

Results

Comparison of the OG and the CG in terms of the general patient data

There were 24 males (55.81%) and 19 females (44.19%) in the OG and 22 males (52.88%) and 20 females (47.62%) in the CG. The males ranged in age from 35 to 75, with a mean age of (42.58±1.25), and the females ranged in age from 36 to 74, with a mean age of (42.56±1.23). The operation times and the intraoperative amount of bleeding ranged from 52-96 min and 81-159 ml in the OG, with mean values of (68.96±3.15) min and (97.02±2.58) ml and 53-98 min and 82-158 ml in the CG, with mean values of (69.06±3.13) min and (97.01±2.53) ml. 21 patients in the OG were injured on the left knee, and 22 on the right knee, accounting for 48.84% and 51.16% respectively, and in the CG, the corresponding values were 23 (54.76%) and 19 (45.24%). No statistical differences were found between the OG and the CG in terms of gender, age, operation time, intraoperative amount of bleeding, or site of the injury (P>0.05, **Table 1**).

Comparison of the OG and the CG in clinical efficacy

In the OG, 18 patients were cured, and the treatment was demonstrated to be markedly effective in 15 cases, effective in 8 cases, and ineffective in 2 cases, for a total effective rate of 95.35%, which exceeded the CG (P<0.05, **Table 2**).

Comparison of the OG and the CG in the formation of venous thrombus

The venous thrombus formation rate was 2.33% in the OG and 21.43% in the CG (P< 0.05, **Table 3**).

Comparison of the OG and the CG in terms of their coagulation function indices

Before the treatment, the PT was (10.02±0.42) s in the OG and (10.08±0.39) s in the CG

Table 3. Comparison of the OG and the CG in the formation of venous thrombus [n (%)]

Group	n	Rate of venous thrombus formation
CG	42	9 (21.43)
OG	43	1 (2.33)*
X^2		7.469
P		0.006

Note: *represents P<0.05 as compared with CG.

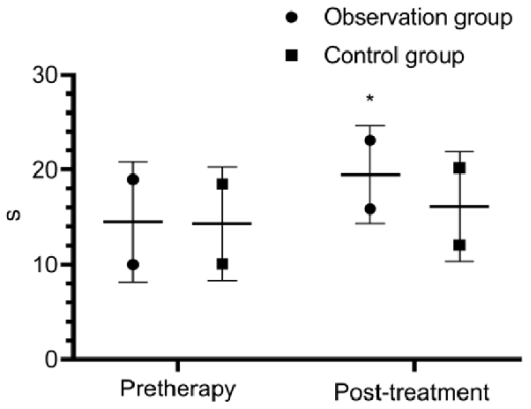

Figure 1. Comparison of the OG and the CG for PT. Before treatment, no statistical difference was found between the OG and the CG for PT (P>0.05); after treatment, the PT was longer in the OG as compared with the CG (P<0.05). * indicates P<0.05 compared with CG.

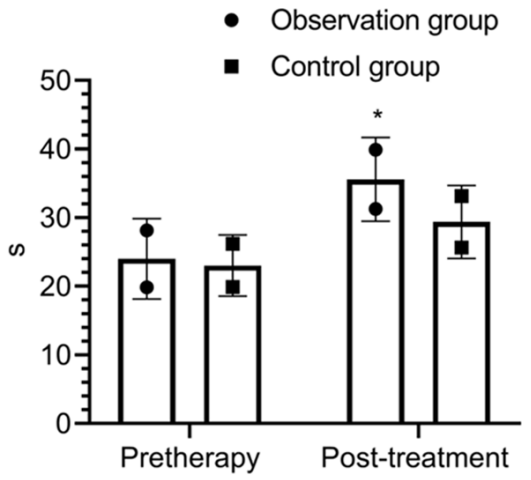

Figure 2. Comparison of the OG and the CG in APTT. The two groups were observed and compared in their APTT before and after the treatment. Before the treatment, they were almost the same (P>0.05), but after the treatment, the OG reported a longer APTT than the CG (P<0.05). * indicates P<0.05 compared with the CG.

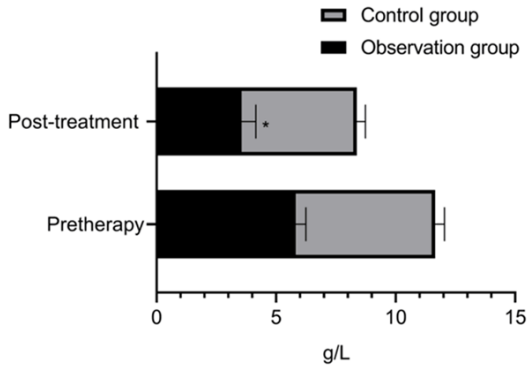

Figure 3. Comparison of the OG and the CG in FIB. On the basis of similar values before the treatment (P>0.05), the OG reported a lower FIB than the CG after the treatment (P<0.05). * indicates P<0.05 compared with the CG.

(P>0.05); after the treatment, the PT in the OG extended to (15.85±0.58) s, longer than that of the CG, which was (12.05±0.63) s (P<0.05, **Figure 1**).

The 2 groups demonstrated no statistically significant differences in their APTT before the treatment, which was (19.85±0.52) s in the OG and (19.88±0.49) s in the OG. However, after the treatment, both groups attained an extension to (31.25±0.62) s and (25.63±0.69) s, respectively (P<0.05, **Figure 2**).

In terms of FIB, no statistically significant differences were observed in the two groups before the treatment, and the reported data were (5.52±0.18) g/L in the OG and (5.55±0.15) g/L in the CG (P>0.05); after the treatment, the FIB was reduced to (3.12±0.58) g/L in the OG, and to (4.58±0.49) g/L in the CG (P<0.05, **Figure 3**).

For the DD before treatment it was (1.92±0.15) μg/L in the OG and (1.93±0.14) μg/L in the CG (P>0.05), (1.02±0.08) μg/L and (1.58±0.12) μg/L after treatment (P<0.05, **Figure 4**).

Comparison of the OG and the CG in terms of their platelet indices

No statistically significant differences were found in the 2 groups for PDW, MPV, or PLT (P>0.05), but both groups achieved elevations in PDW and MPV and reductions in PLT after

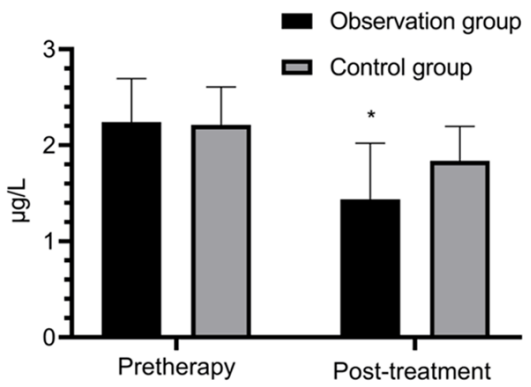

Figure 4. Comparison of the OG and the CG in DD. Before the treatment, the two groups demonstrated no significant difference in their DD (P>0.05); after treatment, the DD reduced in the OG to a level lower than it was in the CG (P<0.05). * indicates P<0.05 compared with the CG.

the treatment (P<0.05); compared with the CG, the OG reported higher PDW and MPV, and lower PLT (P<0.05, **Table 4**).

Comparison of the OG and the CG in their incidences of adverse reactions

During the treatment, the incidences of adverse reactions such as pain at the injection site and gastrointestinal reactions were 2.33% and 4.65% in the OG and 4.76% and 2.38% in the CG (P>0.05); no bleeding was reported in the OG, but in the CG, the bleeding incidence was 19.05% (P<0.05, **Table 5**).

Discussion

Knee arthroplasty is one of the most common operations for knee problems , with its effects extensively recognized [15]. Knee problems are common and have a great possibility of leading to joint deformity or the loss of knee function in serious cases when not treated in a timely effective, or proper way. Knee problems may seriously affect one's daily life, but they also can place a heavy burden on society and on one's family [16, 17].

In the clinic, conservative therapies are preferred by senior patients with knee problems, but they can hardly achieve ideal clinical efficacy [18]. Therefore, knee arthroplasty is extensively applied in the clinic. Though the operation can alleviate the clinical syndromes and improve knee function, it may be followed by a high rate of venous thrombus formation [19, 20]. Presently, methods to prevent the formation of venous thrombus at home and abroad include medicines, exercises, and habits, of which, medicines are the most frequently applied. Clinical medicines adopted to prevent the formation of venous thrombus include general heparins, warfarin, and LMW heparin [21]. Though the general heparins have been applied in the prevention of venous thrombus formation for a rather long period of time with a certain efficacy, they easily cause bleeding, thrombocytopenia, etc. [22]. Warfarin is not for routine use as it, can lead to bleeding if not properly used [23]. For patients with coagulation dysfunctions, thrombocytopenia, and digestive tract ulcers, which may lead to bleeding, their actual conditions will determine their treatment with anticoagulants. The bleeding risk should be evaluated before administering the drug. LMW heparin is a new drug that guards against the formation of venous thrombus. Compared with general heparins, it has a longer half-life and is safer, such that instead of extending the bleeding time, it can reduce bleeding [24].

Patients who undergo operations due to fractures have to lie in bed for a rather long time, during which, they are prone to venous thrombus. In recent years, with the population aging in China, the number of patients undergoing knee arthroplasty is increasing [25]. Studies have revealed that the incidence of venous thrombus formation after a fracture operation ranges from 40% to 60% [26] if no preventative measures are adopted. Currently, the clinical diagnosis and treatment of venous thrombus formation are not very optimistic. According to the results of this study, the total effective rate in the OG was higher than it was in the CG, but the formation rate of venous thrombus in the OG was lower than it was in the CG (P<0.05), indicating that compared with heparin sodium injections, LMWH-Na injections i were more effective in preventing and guarding the formation of venous thrombus after knee arthroplasty. The mechanism of action may be that LMWH-Na injection is resistant against the Xa activity such that it can effectively inhibit the formation of arterial and venous thrombus, thrombus *in vitro* and *in vivo* without affecting platelets, fibrinogen binding, or platelet aggregation, which can not only exert antithrombotic effects, but can also reduce the incidence of bleeding. The results of this study showed that PT and APTT in the OG were longer than those in the

Table 4. Comparison of the OG and the CG in the platelet related indices ($\bar{x}\pm s$)

Group	PDW (fL)		MPV (fL)		PLT ($\times10^9$/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
CG (n=42)	12.92±1.52	13.09±1.62#	10.25±1.25	11.12±1.56#	160.28±5.12	148.96±4.25#
OG (n=43)	12.98±1.49	14.58±1.88#,*	10.29±1.23	12.99±1.85#,*	160.32±5.09	132.25±2.18#,*
t	0.184	3.910	0.149	5.032	0.036	22.886
P	0.855	0.002	0.882	0.000	0.971	0.000

Note: #represents P<0.05 compared with the conditions before the intervention; *represents P<0.05 as compared with CG.

Table 5. Comparison of the OG and the CG in the incidence of adverse reactions [n (%)]

Group	n	Pain at the injection site	Gastrointestinal reaction	Bleeding
CG	42	2 (4.76)	1 (2.38)	8 (19.05)
OG	43	1 (2.33)	2 (4.65)	0 (0.00)*
X^2		0.370	0.322	8.609
P		0.543	0.571	0.003

Note: *represents P<0.05 compared with the CG.

CG, FIB, DD, and PLT in the OG were lower than those in the CG, and PDW and MPV in the OG were higher than they were in the CG (P<0.05), suggesting that after the treatment with the LMWH-Na injection, the patients' coagulation function improved significantly. The mechanism of action may be as follows: DD, FIB, APTT, and PT are routine indices adopted clinically to reflect the coagulation function. Shortened APTT and PT indicate hypercoagulation. FIB is a macromolecular protein in the acute phase, which will be generated in large quantities in the case of an operation or trauma and enter the blood, playing a special role in the process of coagulation and hemostasis. DD is a specific marker of crosslinked fibrin produced by the action of plasmin, and its concentration will be significantly increased in the case of acute thrombus. The results of this study indicated that the therapeutic effect of LMWH-Na injection is better than that of heparin sodium injection. In addition, this study also investigated the drug safety. The results demonstrated that the two groups had no statistical differences in terms of the incidences of pain at the injection site or in their gastrointestinal reactions during the treatment (P>0.05); the OG reported a bleeding incidence of 0.00%, far lower than the 19.05% of the CG (P<0.05), indicating that the adoption of LMWH-Na injection to prevent venous thrombus formation can reduce the bleeding rate and improve drug safety instead of adding to the drug-related adverse reactions.

In conclusion, LMWH-Na is more effective at reducing the incidences of venous thrombus and improving the coagulation and platelet functions after knee arthroplasty, with no addition to the drug-related adverse reactions and with increased drug safety.

However, this study was based on a limited sample size. In the future, the sample size will be increased for a more in-depth exploration.

Disclosure of conflict of interest

None.

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