

Comparison of analgesic consumption of hemophilic and non-hemophilic patients in knee arthroplasty

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ABSTRACT

BACKGROUND: Hemophilia is a rare hereditary bleeding disorder that develops as a result of factor VIII or IX deficiency. Long-term complications of hemophilia such as arthropathy, synovitis, and arthritis can lead to the development of recurrent chronic pain. Pain is therefore a critical aspect of hemophilia. The gold standard treatment for end-stage hemophilic knee arthropathy is total knee arthroplasty (TKA). The hypothesis of this study was that after knee replacement surgeries that cause severe post-operative pain, hemophilia patients with chronic analgesic consumption may experience higher levels of pain than non-hemophilic patients, and use more opioid and non-opioid drugs.

METHODS: This retrospective study included 82 patients who were hemophilic and non-hemophilic TKA patients operated under general anesthesia. Seventy-three patients were evaluated and divided into two groups according to the diagnosis of hemophilia: 36 patients were investigated in the hemophilic group and 37 patients in the non-hemophilic group.

RESULTS: Post-operative tramadol consumption ($p=0.002$) and pethidine consumption ($p=0.003$) were significantly higher in the group hemophilia. The length of stay in the hospital was also significantly longer in the hemophilic group ($p=0.0001$).

CONCLUSION: In the light of these informations, we think that acute post-operative pain management of hemophilia patients should be planned as personalized, multimodal preventive, and pre-emptive analgesia.

Keywords: General anesthesia; hemophilia; post-operative analgesia; total knee arthroplasty.

INTRODUCTION

Hemophilia is a rare hereditary bleeding disorder that develops as a result of factor VIII or IX deficiency, showing recessive transition due to chromosome X, and is defined by intra-articular (hemarthrosis) and intramuscular (hematoma) hemorrhages.^[1-4] Factor VIII deficiency is called Hemophilia A, and factor IX deficiency is called Hemophilia B. Hemophilia A constitutes 80% of all hemophilia and occurs one in approximately 5,000–10,000 male births. The FVIII and IX genes are found in the long arm of the X chromosome (Xq27 and Xq28, respectively).^[2]

Hemarthrosis and hematoma are the most typical characteristics of the disease.^[5] The most common bleeding joints in hemophilia are the knee, elbow, and ankle joints. Pain, swelling, redness, increased heat, and limitation of range of motion can be seen. However, pain and movement limitation are the most important symptoms of hemarthrosis.^[6] Bleeding into the joint cavity leads to inflammation of the synovial membrane (synovitis). Proteolytic enzymes in the blood cause degeneration of the joint cartilage and ultimately contraction in the joint cavity. Especially in the target joints (joints bleeding 3 times or more for 6 months), chronic hemophilic arthropathy develops, which is the most common chronic complication

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of hemophilia.^[7] Long-term complications of hemophilia such as arthropathy, synovitis, and arthritis can lead to the development of recurrent chronic pain. Pain is therefore a critical aspect of hemophilia. Chronic pain can lead to chronic opioid usage which also can cause substance abuse to improve pain relief.^[8,9] In this group of patients who develop limitation of range of motion and pain complaints, prosthetic surgeries are needed.^[10,11] After total knee arthroplasty (TKA) surgeries, moderate-to-severe post-operative pain is seen that affects patient satisfaction and general results.^[12] To the best of our knowledge, there are a few studies in the literature investigating post-operative pain in knee arthroplasty in patients with hemophilia.^[13–15]

Our hypothesis in this study is that after knee replacement surgeries that cause severe post-operative pain, hemophilia patients with chronic analgesic consumption may experience higher levels of pain than non-hemophilic patients.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Board of our university hospital with no. 21/01/2021-12. Hemophilic and non-hemophilic TKA patients operated under general anesthesia between 2001 and 2020 were included in the study. All surgeries were performed by same surgeon. Patients whose files were missing or who underwent additional surgery with TKA were excluded from the study. Archived files, perioperative anesthesia forms, hematology consultation forms, and discharge information in the hospital registration system were used to obtain the data.

Demographic data (age, gender, and body mass index (BMI)) of patients were recorded. Operation duration, intraoperative units of blood transfusion, intensive care unit (ICU) length of stay, and hospital length of stay were registered. Intravenous (iv) analgesic doses of paracetamol, tenoxicam, tramadol, and pethidine administered to patients in the post-operative 1st and 2nd days after TKA were noted. If there was no contraindication such as renal or hepatic failure or allergies, after TKA surgeries 4×1 g paracetamol and 1×20 mg tenoxicam were given to the patients if the patient had pain. 1 mg/kg tramadol 4 times a day and 0.5 mg/kg pethidine twice a day administered if the patient needed more analgesic for breakthrough pain.

The path we followed for the operations and the hemostasis protocol is below:

All patients were evaluated by the multidisciplinary Hemophilia Council of our university hospital. Hemostasis tests and viral serological tests were performed for those who were decided to operate. Hemophilic patients were given tranexamic acid tablets 40 mg/kg/day (maximum 2000 mg/day) from 12 h before the operation to post-operative day 10 as 4×1 tablets. Factor replacement therapy was started 2 h

before the operation, for a plasma level of 80%. During intraoperative period, an additional factor dose for 20% increase and 10 mg/kg tranexamic acid were given intravenously. Factor replacement therapy was resumed 4-6 h after the operation. During the first 72 h, 60 IU/kg/day (6–8 doses) Factor VIII was used in Hemophilia A cases and 80–100 IU/kg/day (3–4 doses) Factor IX was used in Hemophilia B patients. The patients were followed up daily or every other day with complete blood count (CBC), activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, and D-dimer tests. Factor VIII/IX and inhibitor levels were checked on the post-operative 3rd, 7th, and 12th days. The doses on days 4–7 were decreased to 40 IU/kg/day for Factor VIII; 60–80 IU/kg/day for Factor IX; on days 8–12 to 30 IU/kg/day for Factor VIII; and 50 IU/kg/day for Factor IX. Then, by giving the same doses every other day, the prophylaxis was performed for another 6 weeks. The patients with bleeding were given an additional dose and the previous step was returned. Additional doses were administered to patients with low factor levels in laboratory controls. Apheresis platelets were given to the patients who continued to bleed and were transfused with more than 3 units of red cell packed. Thrombosis prophylaxis was not performed in any of the patients.

Patients who had general anesthesia for TKA in this study underwent tracheal intubation by administration of 2–3 mg/kg propofol, 1–2 µg/kg fentanyl, and 0.1 mg/kg vecuronium and maintenance was provided by 1-MAC sevoflurane.

Statistical Analysis

SPSS 21. 0 SPSS (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis. Descriptive statistical methods, mean, standard deviation, and frequency were used while evaluating the study data. Student's t-test was used in two group comparisons of quantitative data showing normal distribution and Mann–Whitney U-test was used in two group comparisons of data that did not show normal distribution. Pearson's Chi-square test and Fisher's Exact test were used to compare qualitative data. Logistic regression analysis was used to evaluate parameters affecting the hemophilia patient group. Significance was evaluated at $p < 0.05$.

RESULTS

In this study, the data of 82 patients were evaluated and their eligibility to study was investigated. Of these, 73 patients were included in the study. The remaining nine patients were excluded from the study since three patients underwent additional surgery to TKA, and six patients had deficiencies in their files. According to the diagnosis, patients were divided into hemophilic group and non-hemophilic group. Thirty-six patients were investigated in the hemophilic group and 37 patients in the non-hemophilic group (Fig. 1). The demographic data of the patients are in Table 1. The mean age of the patients was 50.7 ± 17.9 years. The BMI averaged 29.1 ± 5.2 . The

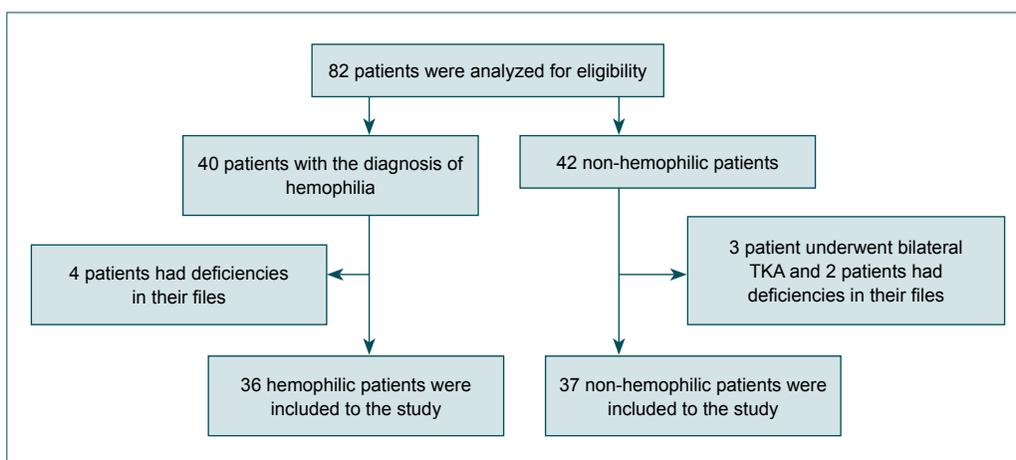


Figure 1. Consort flow diagram.

mean operation duration of TKA was 178 ± 53 min. An average of 0.60 ± 0.73 units of blood transfusion was needed intraoperatively. Patients were in ICU for an average of 0.6 ± 0.8

days and an average hospital length of stay was 16.1 ± 9.1 days. For post-operative analgesia, an average of 2.5 ± 0.9 g paracetamol, 23.3 ± 22.4 mg tenoxicam, 51.6 ± 73.2 mg pethidine, and 166.7 ± 91.1 mg tramadol was given. The descriptive and perioperative clinical characteristics of the patients are given in Table 1.

Table 1. Demographic data of the study

Age (year)	50.72±17.94
Gender (female/male), n (%)	32 (43.8)/41 (56.2)
Body mass index	29.07±5.17
Operation duration (min)	178.31± 53.08
Transfusion (unit)	0.60±0.73
Hospital length of stay (day)	16.06±9.08
ICU length of stay (day)	0.64±0.80
Pethidine usage (mg)	51.64±73.23
Tramadol usage (mg)	166.71±91.12
Tenoxicam usage (mg)	23.28±22.36
Paracetamol usage (g)	2.47±0.89

ICU, intensive care unit. Table show mean±standard deviation.

Cross-group comparisons are shown in Table 2. Average age of hemophilia group was significantly lower than non-hemophilic group with a value of 34.8 ± 8.0 years ($p=0.0001$). When cross-group comparisons were made, it was determined that the average age of group hemophilia was significantly lower than non-hemophilic group with a value of 34.8 ± 8.0 years ($p=0.0001$). BMI was also significantly lower in group hemophilia ($p=0.004$) (Table 2).

Operation duration was significantly longer in hemophilic group with 203 ± 57 min ($p=0.0001$). While the non-hemophilic group did not need any blood transfusions in the intraoperative process, it was observed that 0.6 ± 0.7 units of blood transfusion were needed on group hemophilia, which

Table 2. Comparison between groups

	Hemophilic group (n=36)	Non-hemophilic group (n=37)	p-value
Age (year)	34.81±8.01	66.21±9.04	0.0001*
Body mass index	27.35±5.71	30.74±3.99	0.004*
Operation duration (min)	203.82±57.19	154.86±36.06	0.0001*
Transfusion (unit)	0.60±0.73	0	0.0001*
Hospital length of stay (day)	21.94±9.24	10.35±3.72	0.0001*
Intensive care unit length of stay (day)	0.75±0.81	0.54±0.81	0.270
Pethidine usage (mg)	76.94±92.17	27.02±34.71	0.003*
Tramadol usage (mg)	198.88±90.92	135.40±80.78	0.002*
Tenoxicam usage (mg)	24.44±24.89	22.16±19.87	0.667
Paracetamol usage (g)	2.55±1.08	2.40±0.68	0.480

Table show mean±standard deviation. *P<0.05 considered as significant.

Table 3. Regression analysis

	Beta	Adjusted R Square	Significance (p<0.05)	95.0% Confidence Interval for B	
				Lower Bound	Upper Bound
Age (year)	-0.025	0.773	0.0001	-0.022	-0.028
Body mass index	-0.032	0.096	0.004	-0.010	-0.054
Operation duration (min)	0.004	0.204	0.0001	0.006	0.002
Hospital length of stay (day)	0.036	0.404	0.0001	0.046	0.026
Pethidine usage (mg)	0.003	0.105	0.003	0.005	0.001
Tramadol usage (mg)	0.002	0.111	0.002	0.003	0.001

was statistically significant ($p=0.0001$). While there was no significant difference in ICU length of stay between both groups, hospital length of stay for the group hemophilia was significantly longer ($p=0.0001$) (Table 2).

Although the doses of paracetamol and tenoxicam used in post-operative analgesia were similar between both groups, tramadol consumption ($p=0.002$) and pethidine consumption ($p=0.003$) were significantly higher in group hemophilia (Table 2). The regression analysis supporting our data can be seen at Table 3.

DISCUSSION

In this retrospective study, it was found that the consumptions of tramadol ($p=0.002$) and pethidine ($p=0.003$) as post-operative analgesics after TKA were significantly higher in hemophilic group. Pain unresponsive to analgesic use is the most common indication for TKA, which is considered the gold standard treatment for end-stage hemophilic arthropathy in the hemophilic group.^[16–19] Hemophilia is complicated with both acute pain during bleeding episodes and chronic pain caused by arthritic complications of recurrent bleeding.^[20,21] Increased pain sensitivity in patients is associated with the severity of joint pathology. Goddard et al.^[22] review that should be aware of hemophilia patients' need for high-dose opioids for a longer time in the post-operative period. For these reasons, pain management becomes more difficult in hemophilic patients. The studies on general population undergoing TKA show that peripheral blocks (femoral, sciatic, and interspace between the popliteal artery and posterior capsule of the knee- IPACK) ensure a better post-operative analgesia while avoiding the side effects of IV opioid analgesics such as sedation, respiratory depression, nausea, and vomiting which can lead to delayed mobilization and longer hospital length of stay.^[23–26] Conventionally, peripheral blocks are contraindicated in hemophilic patients. However, there are studies about using peripheral blocks for anesthesia and post-operative analgesia in hemophilic patients. They showed that optimizing the factor levels peripheral blocks can be performed safely and contain a better post-operative analgesia.^[13,27,28]

In this study, we found that the group of hemophilic patients was younger ($p=0.0001$) and BMI in this group was also significantly lower ($p=0.004$). Due to recurrent hemarthroses in hemophilia patients, degenerative joint disease progresses more rapidly and end-stage hemophilic arthropathy develops in younger ages than the non-hemophilic population.^[29,30]

There was no significant difference in the ICU length of stay of the patients. Due to the increase in post-operative complications and post-operative pain management difficulties, the length of stay in the hospital was significantly longer ($p=0.0001$) in hemophilia patients who underwent TKA under general anesthesia compared to non-hemophilic patients.^[29] TKA surgeries are technically challenging in the hemophilic group and longer operation durations are observed ($p=0.0001$). Blood transfusion amounts are also higher as expected ($p=0.0001$). It has been shown in various studies that post-operative complications such as infection, pulmonary thromboembolism, deep vein thrombosis, and cardiac and neurological complications are increased in hemophiliacs.^[31–34]

The first of the limitations of our study is the differences in the demographic data between groups. Hemophilia patients are all men due to showing recessive transition due to X. The hemophilic group is younger and has a lower BMI, because they need TKA in younger ages as a result of the recurrent hemarthrosis. In non-hemophilic population, arthropathies are seen in older people. It is hard to find patients in non-hemophilic group with similar demographic data as hemophilic patients. Second, our study is designed retrospectively. Third, it can be considered that the study is single-centered and, therefore, contains a small number of patients. Another limitation of this study, intravenous patient-controlled analgesia, has not been utilized to optimize pain. However, at the same time, our hospital has an experienced team that follows hemophilia patients together with orthopedics, hematology and anesthesia clinics.

Conclusion

In the light of these informations, we think that acute post-operative pain management of hemophilia patients should be

planned as personalized, multimodal preventive, and preemptive analgesia. Regional anesthesia can also be an alternative. We think optimizing the factor levels and with ultrasound guidance femoral, sciatic, and IPACK blocks that can be used for post-operative analgesia in hemophilic patients undergoing TKA so that increased opioid use and its side effects can be avoided.

Ethics Committee Approval: This study was approved by the İstanbul University İstanbul Faculty of Medicine Ethics Committee (Date: 21.01.2021, Decision No: 12).

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ORIJİNAL ÇALIŞMA - ÖZ

Diz artroplastilerinde hemofilik ve non-hemofilik hastaların analjezik tüketimlerinin karşılaştırılması

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AMAÇ: Hemofili, faktör VIII ya da IX eksikliği sonucu gelişen, nadir, herediter bir kanama bozukluğudur. Artropati, sinovit ve artrit gibi hemofilinin uzun dönem komplikasyonları tekrarlayıcı kronik ağrı gelişimine yol açabilir. Bu nedenle ağrı, hemofilinin kritik bir yönüdür. Son dönem hemofilik diz artropatisi için altın standart tedavi total diz artroplastisidir. Bu çalışmanın hipotezi; diz replasman cerrahisi sonrası, kronik analjezik tüketimi olan hemofilik hastaların hemofilik olmayan hastalara göre daha yüksek ağrı düzeyleri deneyimleyeceğidir.

GEREÇ VE YÖNTEM: Bu geriye dönük çalışmaya, genel anestezi altında ameliyat edilmiş hemofilik ve hemofilik olmayan total diz artroplastisi hastası 82 hasta alındı. Yetmiş üç hasta değerlendirmeye alındı ve hastalar hemofili tanısı olup olmamasına göre 2 gruba ayrıldı: 36 hasta hemofili grubunda ve 37 hasta hemofilik olmayan grupta incelendi.

BULGULAR: Ameliyat sonrası tramadol ($p=0.002$) ve petidin tüketimi ($p=0.003$) de hemofilik grupta anlamlı olarak daha yüksekti. Hastane yatış süresi hemofilik grupta anlamlı olarak daha uzundu ($p=0.0001$).

TARTIŞMA: Bu bilgiler ışığında, hemofili hastalarının akut ameliyat sonrası ağrı yönetiminin, kişiye özel, multimodal ve önleyici bir analjezi olarak planlanması gerektiğini düşünmekteyiz.

Anahtar sözcükler: Ameliyat sonrası analjezi; genel anestezi; hemofili; total diz artroplastisi.

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