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Research Article

Undertreatment of Hepatitis C Virus Infection in Elective Total Hip Arthroplasty

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1. Abstract

1.1. Background: Total Hip Arthroplasty (THA) in patients with hepatitis C virus (HCV) are known for poor outcomes increased risk of iatrogenic infection. New Direct Antiviral Agents (DAA) can now cure HCV infection. However, undertreatment is still common in patients undergoing THA. Our aim was to assess the prevalence of HCV infection and treatment rates in patients with detectable RNA. We compared perioperative complications between HCV infection and non-HCV infection at the minimum one year follow-up.

1.2. Methods: Between 2003 and 2018, 3574 patients (4518 hips) who had undergone THA at two hospitals were enrolled. Patients were stratified into two groups: (1) HCV-Ab negative serology (2) HCV-Ab positive serology. Treatment history for HCV infection was analyzed by reviewing medical record. Perioperative outcomes including intraoperative bleeding, transfusion rate, operation time, hospital stay, postoperative infection, and revision for 1year follow up was analyzed.

1.3. Results: Among 3317 patients, 47 patients (1.4%) were positive for anti-HCV, and eight patients (0.2%) had detectable RNA load. Of the 47 patients, only 20 patients had HCV infection whereas the remaining 27 patients were diagnosed during preoperative assessment. Six patients reported treatment. Two of eight patients (25%) underwent DAA treatment after THA. Patients with HCV infection had a higher rate of transfusion, infection, and revision. A multivariate analysis with logistic regression model showed that HCV infection was a significant risk factor for postoperative infection and revision.

2. Keywords: Hepatitis C; Direct antiviral agents; Total hip arthroplasty; Orthopedics; Infection

3. Introduction

Total Hip Arthroplasty (THA) is a safe, successful, and reproducible elective surgical procedures in patients with end stage hip disease [1]. There is growing evidence that patients undergoing THA, who are diagnosed with hepatitis C virus (HCV) infection are at high risk for postoperative complications, such as periprosthetic joint infection and revision surgery. Chronic HCV infection is associated with several complications following THA, including Periprosthetic Joint Infections (PJIs), blood loss, and wound-healing complications. HCV is associated with the deposition of cryoglobulins, a cold-insoluble immune complex, in the vascular endothelium of small and medium-sized vessels leading to a vasculitis that impairs tissue perfusion [17]. In addition to host complications, active HCV infection endangers the safety of physicians and members of the surgical team.

Recently, according to the advent of Direct-Acting Antiviral (DAA) treatments, patients may benefit from unprecedented cure rates in excess of 90%. The use of these novel curative the-

rapeutic agents, may render HCV a potential modifiable risk factor that can be addressed before THA [6, 7]. However, the prevalence and treatment rates of HCV infection after THA are rarely reported.

Therefore, the purpose of this work was to assess the prevalence of HCV infection and treatment rates in patients with detectable RNA positive HCV infection. In addition, we compared perioperative complications after THA between HCV and non-HCV patients at the minimum one year follow-up.

4. Materials and Methods

4.1. Patient Selection and Data Collection

The design and protocol of this retrospective study were approved by the Institutional Review Board of Chung-Ang University Hospital.

This study included 3574 patients (4518 hips) who had undergone THA at two hospitals between 2003 and 2018. After exclusion of 260 patients who had THA for acute hip fracture, 3314 patients (1644 men and 1670 women) who received elective THA procedures were analyzed (Figure 1). Liver function and HCV infections status before THA were assessed using serum liver enzyme levels and HCV antibody (HCV-Ab) screening tests in all patients. Patients who were positive for HCV-Ab serology were further evaluated for HCV-RNA. The mean age at the time of surgery was 54.4 years (range: [16-104]) and patients were followed for a minimum of one year after index surgery (Figure 1).

Patients were further stratified in to two groups: (1) 3267 patients who were negative for anti-HCV serology (Group I), (2) 47 patients who were positive for anti-HCV serology (Group II). Group II was further divided into two subgroups: 39 patients who were negative in theHCV RNA assay (Group IIa) and eight patients who were positive in the HCV RNA assay (Group IIb) (Figure 1).

A diagnosis of HCV infection was established by performing a HCV serology test and detecting HCV RNA using guidelines from the Korean Association for the Study of Liver (KASL). The quantitation range of the HCV RNA assay (CAP-CTM; Roche) was 21 to 6.9 x 107 IU/mL; therefore, values lower than 21 IU/mL were undetectable.

In group Group IIa and Group IIb, after reviewing medical records, eight patients underwent antiviral treatment for HCV infection. Among these eight patients, six were treated before surgery while the remaining two patients were treated after THA. In addition, two of the six patients who had treatment for HCV infection prior to the surgery were still positive for the RNA assay in preoperative analysis (3,294,000 and 3,400,000) (Figure 1).

Demographic data, including age, gender, diagnosis, Body Mass Index (BMI), American Society of Anesthesiologists score (ASA score), medical comorbidities on the bases of the modified Charlson's Comorbidity Index(CCI), previous intensive care unit admission, operation time, blood loss, transfusion rate, and length of hospital stay were obtained by reviewing medical records (Table 1).

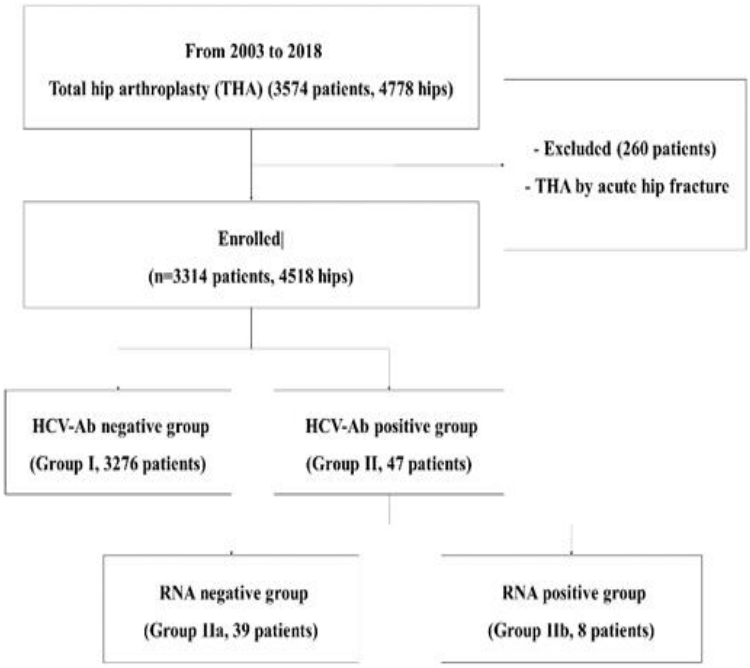

Figure 1

Table 1: Comparison of demographic data between Group I and Group II.

	Group I (n = 3276)	Group II (n = 47)	*P*-value
Age (years) ± SD	54.36±14.93	59.77±14.29	0.013
Gender (male: female)	1628(49.7%)/1648(50.3%)	16(34.5%)/31(65.5%)	0.029
BMI ± SD	24.60±3.60	25.39± 3.89	0.171
ASA score±SD	1.65±0.61	1.57±0.83	0.517
CCI ± SD	0.67±1.17	1.79±0.86	<0.001
Diagnosis			
ONFH	1749	20	
Primary OA	450	13	0.09
Secondary OA	991	13	
Inflammatory arthritis	104	8	
Others	73	0	

ONFH : Osteonecrosis of femoral head, OA : osteoarthritis, SD : standard deviation

Routine follow-up visits were scheduled at 6 weeks and; 3, 6, 9, and 12 months. Patients who were unable to attend follow-up evaluations were interviewed by telephone. Clinical information was collected by 1 orthopedic surgeon and 2 nurses. Outcome analysis, including perioperative complications and treatment of HCV infection, were

conducted by comparing Group I and Group II. Further subgroup analysis between Group IIa and IIb were performed to compare complications such as infection, dislocation, and revision after THA.

5. Statistical Analysis

The prevalence of HCV infection in elective THA patients was calculated and compared with the prevalence of Hepatitis C in the general population of South Korea [1]. Demographic data such as sex, age, BMI, diagnosis, medical comorbidities based on ASA score and CCI, were compared between Group I and II. Additionally, perioperative factors relating to HCV infection, including operation time, transfusion rate, blood loss, length of hospital stay, postoperative ICU care, infection, and any kind of revision, were also compared between the two groups. Categorical variables were analyzed using the chi-square or Fisher exact test and numerical variables were used in the T-test. Further subgroup analysis was performed between Group IIa and IIb.

To assess the effect HCV infection in perioperative infection, multivariate analysis was performed. Variables that had P value <0.10 (age, gender, ASA and CCI scores) were included in the multivariate model. Statistical analysis was performed using IBM SPSS Statistics version 23.0 (IBM, Chicago, IL, USA). All two-sided P values <0.05 were considered statistically significant.

6. Results

Among the 3317 patients enrolled in this study, 47 (1.4%) were positive for anti-HCV serology. In a further assessment using the HCV RNA assay, HV RNA was detected in eight patients with mean viral load of $1.686 \times 106 \pm 1 \times 106$ (range $3.659 \times 105 – 3.4 \times 106$) IU/mL. Out of these 47 sero positive patients, only 20 were aware of their HCV infection status whereas the remaining 27 patients were diagnosed during the preoperative assessment. According to the medical histories, four patients reported interferon treatment and two patients reported treatment with direct antiviral agents (DAA) after THA. One patient was still positive for HCV RNA at the index operation. (Table 2).

The transfusion rate (P =0.020), Age (P = 0.013), rate of female gender (P = 0.029), CCI scores (P = 0.020), revision for any reason (P = 0.003), and infection (P = 0.010) were significantly higher in Group II than in group I. During follow-up, perioperative infection occurred in 11 patients (0.3%) (Nine patients (0.3%) in Group I and two (4.3%) in Group I). Furthermore, 22 patients (0.66%) underwent revision for any reason during follow up (19 patients (0.6%) in Group I and three patients (6.4%) in Group II). However, there were no differences in BMI (P = 0.171), diagnosis for surgery (P = 0.090), and ASA score (P = 0.400) between the two groups (Table 2). Multivariate analysis using a logistic regression analysis model showed that postoperative infection (OR=6.376, 95% CI, 1.123-36.183, P = 0.037) and revision for any reason (OR=6.913, 95% CI, 1.826-26.173, P = 0.004) were significant risk factors affected by HCV infection (Table 3).

Table 2: Comparison of intraoperative and perioperative results between Group I and Group II.

	Group I (n =3276)	Group II (n = 47)	*P*-value
Blood loss ± SD (mL)	1139±600	1207±856	0.409
Transfusion	1740(53.1%)	33(69.1%)	0.020
Operation time ± SD (min)	122±42	122±39	0.994
Hospital stay ± SD (days)	11.4±5.6	12.7±5.5	0.329
ICU admission	15(0.5%)	0(0%)	<0.001
Infection	9(0.3%)	2(4.3%)	0.010
Revision	19(0.6%)	3(6.4%)	0.003
ICU : intensive care unit, SD : standard deviation			

Table 3: Multivariate regression for postoperative infection between Group I and Group II

	OR (95% CI)	*P*-value
Postoperative infection		
Hepatitis C	6.589 (1.145-37.914)	0.035
Age	1.090 (1.033-1.151)	0.002
CCI	1.625 (1.154-2.289)	0.005
Postoperative revision for any reason		
Hepatitis C	6.913 (1.826-26.173)	0.004
Age	1.053 (1.016-1.091)	0.005
CCI	1.373 (1.056-1.785)	0.018
ASA score: American Society of Anesthesiologists score, CCI: Charlson's Comorbidity Index		

There were no significant differences in infection or revision rate between Group IIa and Group IIb. One revision in Group IIb was performed because of mal seating of a ceramic liner, which was not related to HCV infection.

7. Discussion

Although HCV may be considered a modifiable risk factor of perioperative complications after THA due to the advent of DAA, the lack of awareness of individual HCV status' and the lack of treatment in elective THA patients is a major concern. We found that 47 out of 3,314 patients (1.4%) were sero positive for HCV positive and eight patients (0.2%) were positive for HCV RNA. Of these patients, only seven had a history of antiviral treatment for HCV infection and two patients were still positive for HCV RNA. In addition, HCV sero positive patients had a significantly higher rate of perioperative transfusion, infection, and revision rate than the control groups.

So far, the reported prevalence of HCV infection in the West ranges from 3% to 8% in orthopedic patients, many of whom may undergo lower extremity total joint arthroplasty [2-5]. The prevalence of HCV infection in this study is 1.4% in patients with elective THA, which is slightly lower than that in previous studies. However, a simple comparison of the prevalence of HCV infection might not

be appropriate because of the differences in demographics, including age, gender, and diagnosis, ethnicity, and disease entity. For example, HCV prevalence is different between countries, owing to ethnicity. Additionally, patients with a history of substance abuse or multiple transfusions have a higher prevalence of HCV. Moreover, an HCV infection rate of 1.4% in patients with elective THA is higher than that in the general population in South Korea (0.62% - 0.78%) [1].

Of the 47 patients who tested positive for the HCV antibody, only 42.5% (20 patients) were known to have hepatitis C, and six of these patients had antiviral agent treatment preoperatively. Further assessment showed that 17% (8 patients) were positive for HCV RNA, one of which had a previous history of interferon treatment. During follow-up periods, only two patients had undergone antiviral agent treatment. One patient had undergone treatment with direct antiviral agents (DAA) after surgery whereas the other, had a history of failure of antiviral agent treatment during the postoperative period. The same patient was retreated with an antiviral agent 4 years after index surgery. Both patients were successfully treated. Neglected treatment of HCV infection in patients for THA was commonly observed in this study. Recently, the introduction of new DAA has led to excellent treatment rate (90%) and short treatment duration (8 - 12 weeks) for hepatitis C infected patients [6-8]. DAA have been available since 2015 in South Korea. In this study, four out of eight patients (two patients before surgery and two patients after surgery) were treated with new DAA and reached sustained virologic response (SVR). In spite of these excellent treatment results with new DAA, many orthopedic surgeons and patients are still not aware of them. Further studies are required to improve SVR rates of HCV infection in patients who are planning elective THA.

For perioperative outcomes, group II patients had a higher rate of transfusion and infections during and after surgery. These findings are concurrent with previous studies. In a meta-analysis of ten studies investigating the outcomes of total joint arthroplasty of HCV infected patients. Wei et al. found that, patients undergoing THA with hepatitis C had a longer hospital stay, higher infection rates, and revision rates [9]. Chronic hepatitis C patients are at a higher risk of bleeding complications secondary to underlying thrombotic micro angiopathy and higher levels of antiphospholipid antibody [10, 11]. For postoperative outcomes, patients in Group II had significantly higher infection and revision rates. Furthermore, in multivariate analysis, adjusting for age, and gender CCI scores, patients in Group II had significantly higher risk of postoperative infection and revision, which is similar to results from previous studies [9, 12-14]. Patients with HCV infection were shown to be at an increased risk of perioperative complications, and HCV treatment led to improved results after elective THA. However, in the subgroup analysis, there were no statistical differences in perioperative outcomes between Group IIa and IIb. Previous studies have shown that patients that undergo THA with detectable HCV RNA have a higher rate of infection (11.7% in HCV RNA positive group vs. 4.2% in HCV RNA negative group) and revision (12.9% in HCV RNA positive group vs. 5.2% in HCV RNA negative group) [6]. Considering the rates of infection and revision in this study, the sample size of HCV RNA positive patients has to be more than 151 to have sufficient power (95%). In this study, there were only 8 patients who were positive for HCV RNA. Considering the prevalence of HCV infection in South Korea (0.62 - 0.78%) [1], more than 15,359 patients undergoing THA need to be evaluated to have sufficient power. Therefore, further multicenter studies with sufficient sample size are required.

In summary, for elective THA, we recommend that patients with positive HCV antibody result should be further analyzed for HCV RNA. If the RNA assay result shows that a patient requires treatment, antiviral therapy should be undertaken before THA to reduce the risk of complications.

We recognize that this study has several limitations. First, a retrospectively designed two center study may increase the risk of selection bias and the effects of unmeasured confounders. Second, one–year follow-up is not enough to evaluate outcomes. However, complications regarding HCV infections mostly occur in the perioperative period. In terms of perioperative complication, one-year follow-up periods might be enough to estimate outcomes regarding infection, bleeding, and transfusion. Finally, according to our study, operation time, ICU admission rate, and length of hospital stay were not significantly different between the two groups. This result differs from previously published data that reported negative outcomes in HCV infected patients [15-17]. We think this difference is due to the small number of hepatitis C patients. Considering retrospective power analysis with prevalence of HCV infection in general population, approximately 1300 patients with HCV infection are required to evaluate valuable postoperative outcomes.

8. Conclusion

Although the prevalence of hepatitis C infection and HCV RNA is 1.4% and 17%, respectively. Only 25% of patients with HCV RNA have undergone DAA treatment. Therefore, surgeons and patients should be aware of undertreatment and negative surgical results of hepatitis C patients, and recommend treatment before THA.

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