

Research Article

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Study on correlation between bone marrow edema, stage of necrosis and area ratio of necrosis with the hip pain grading in nontraumatic osteonecrosis of the femoral head

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Abstract: The objective of this study was to explore the correlation between bone marrow edema, stage of necrosis, and area ratio of necrosis with the hip pain grading in non-traumatic osteonecrosis of the femoral head. Bone marrow edema grading at all levels and the hip pain grade differences were statistically significant ($P < 0.001$). Bone marrow edema grading increased by levels of 0, 1, and 2, whereas average pain rating increased as well to 40.73, 104.66 and 143.49. I ~ III period stage of necrosis and the hip pain grade difference was statistically significant ($P < 0.001$), with the average grade progress pain stage by the death of a rank gradually increased, I period, II period, III period was 57.00, 88.58 and 120.62, respectively. Area ratio of necrosis between 0 ~ 3 were positively correlated with pain, compared the two was statistically significant ($P < 0.001$), and with the degree of pathological changes is aggravating, increase the average rank of levels of pain. 0, 1, 2 and 3 are 36.88, 98.03, 123.87 and 151.93 respectively. We can choose the treatment method and evaluate treatment effect by considering a patients' degree of bone marrow edema, stage of necrosis and area ratio of necrosis.

Keywords: Pain grading, Bone marrow edema, Stage of necrosis, Area ratio of necrosis

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1 Introduction

Ischemic necrosis of the femoral head (INFH) can be classified into traumatic osteonecrosis of the femoral head (TONFH) and non-traumatic osteonecrosis of the femoral head (NONFH) according to etiology [1]. The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in term of such damage” [2]. In 1995, the American Pain Society (APS) listed pain as the fifth vital sign [3]. Pain is not only the focus of diagnosis and treatment in traditional Chinese medicine, but also the main reason for many visits as well as the main symptom in NONFH patients, whose influence on patients' body and mind cannot be ignored. Because of pain, patients are often unable to live a normal life or work normally; pain is also the main reason forcing patients to eventually choose joint replacement. Patients are unable to bear weight due to pain, and because they cannot bear weight, their bone mass decreases, thereby forming a repetitious cycle. However, the cause of NONFH pain is still unclear [4] and research on the cause of hip pain in NONFH is still in the exploratory stage. Scholars have already explored the correlation between bone marrow edema and pain, but pain is not associated with bone marrow edema alone. Review of relevant literature finds that pain may also be associated with stage of necrosis and ratio of necrotic area [1,4,5]. We attempt to retrospectively analyze 168 patients (191 hips) with NONFH who were treated in either the inpatient or outpatient department of Dalian university affiliated Zhongshan hospital of TCM/Affiliated Hospital of Chengdu University of TCM between January 2012 and January 2014, and had complete medical records. The association of hip pain with bone marrow edema, stage of necrosis and ratio of necrotic area in NONFH patients is explored, and possible factors related to hip pain in NONFH patients are further verified, so as to deepen the understanding of hip pain-related factors in NONFH patients. The study is reported below.

2 Clinical Data

2.1 General Information

168 NONFH patients (191 hips) with complete information were systematically analyzed. Among them, 111 were males, and 56 were females; their ages ranged between 20~71 years, with an average age of 45.2 years. Their disease course ranged from 20 days to 10 years. Main symptoms were all unilateral or bilateral hip pain. 37 patients had a history of long-term or high-dose glucocorticoid use; 57 patients had a history of long-term alcohol abuse; 9 patients had histories of long-term alcohol abuse and hormone use; while 7 patients had other unknown complications. Patients with incomplete records and TONFH patients were excluded.

Ethical approval: The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Informed consent: Informed consent has been obtained from all individuals included in this study.

2.2 Imaging Examination and Evaluation Criteria

Patients' medical records were consulted by the HISS system. All patients underwent MRI at our hospital in a supine position with Signa 750 3.0T MRI system (GE, USA). Scanned sites included bilateral acetabulum and femoral head; slice thickness was 4 mm, and scanning was performed continuously at an interval of 1 mm. MRI scanning techniques and parameters: T1WI (TR = 540 ms, TE = 15 ms); T2WI (TR = 3705 ms, TE = 85 ms); STIR (TR = 4300 ms, TE = 120 ms). MRI and X-ray images were evaluated independently by two joint specialists using double-blind method. This approach, combined with medical history and clinical manifestations led to the patients' diagnosis of NONFH.

2.3 Pain Grading Standards

Hip and groin pain described by patients were classified into three grades according to VAS pain scores combined with verbal rating scale (VRS) [6]. Grade 0: VAS 0 point, no pain or occasional mild discomfort; Grade 1: VAS 1-3 points, mild pain but endurable, basically able to live a

normal life, but slightly limited; Grade 2: VAS 4-10 points, moderate to severe pain which is difficult to endure, and affects normal life.

2.4 Bone Marrow Edema Grading Standards

When MRI showed blurred edges in the peripheries of osteonecrotic foci, femoral neck, intertrochanteric region and upper femoral shaft, and low signal on T1WI, high signal on T2WI and clear high signal on STIR, bone marrow edema was considered. Bone marrow edema was classified into three grades according to edema grading method based on T2W1+fat suppression images scanned in coronal position. Grade 0: no bone marrow edema, or confined to foci; Grade 1: bone marrow edema is confined to the femoral head and neck area; Grade 2: bone marrow edema extends from femoral head to subtrochanteric region.

2.5 Osteonecrosis Staging

Osteonecrosis was described according to the Association Research Circulation Osseous (ARCO) staging system for osteonecrosis [7] into stages I-IV.

2.6 Ratio of Necrotic Area Grading Standards

According to Zhao Fengzhao et al.'s [5] method of necrotic area calculation on MRI, ratio of osteonecrotic area equals to the total necrotic area divided by femoral head area multiplied by 100%. This and their experimental results led to the ratio of necrotic area, graded as follows. Grade 0: necrotic area ratio of 0~4.9%; Grade 1: necrotic area ratio of 4.9%~33.6%; Grade 2: necrotic area ratio of 33.6%~41.7%; Grade 3: necrotic area ratio of 41.7%~93.6%. Calculation formula was as follows:

proportion of necrotic area =

$$\frac{\frac{\alpha_1}{360} \times 2\pi rh + \dots + \frac{\alpha_n}{360} \times 2\pi rh}{\frac{\beta_1}{360} \times 2\pi rh + \dots + \frac{\beta_n}{360} \times 2\pi rh} = \frac{\alpha_1 + \dots + \alpha_n}{\beta_1 + \dots + \beta_n} \times 100\%$$

Note: α was the necrotic angle of each slice, β was the circle center corresponding to femoral head on that slice, r was the radius of femoral head, and h was the distance between two MRI slices [5].

2.7 Statistical Methods

Statistical analysis was performed using the SPSS 19.0 statistical package. Correlations of pain grading with bone marrow edema grading, necrosis staging, and ratio of necrotic area grading were analyzed, by χ^2 test for contingency tables and by rank sum test for independent samples. Pain grading for three bone marrow edema grades, pain grading in various necrotic stages and pain grading for ratio of necrotic area grades were pairwise compared by χ^2 test, and analyzed by rank sum test for independent samples. $P < 0.05$ was considered statistically significant.

3 Results

3.1 Correlation between bone marrow edema grading and hip pain grading in patients

In this study, hip pain occurred in 124 hips, with an incidence of 64.92%. Among 52 hips absence of bone marrow edema, only 4 hips (7.69%) had hip pain. Among 96 hips with grade 1 bone marrow edema, 77 hips (80.20%) had hip pain; while among 43 hips with grade 2 bone marrow edema, hip pain occurred in all 43 hips (100%). A contingency table χ^2 test between bone marrow edema grading and pain grading suggested a correlation between bone marrow edema grading and pain grading ($P < 0.001$). Correlation of grade 0 bone marrow edema with pain grading was significantly different from that of grades 1 and 2 ($P < 0.001$); while no statistically significant difference was found between grades 1 and 2 ($P > 0.05$). Differences in pain grading among various grades of bone marrow edema were statistically significant ($P < 0.001$). With the aggravating bone marrow edema, mean ranks of patients' hip pain grading increased gradually, which were 40.73, 104.66 and 143.49, respectively, for grades 0, 1 and 2 (Table 1).

3.2 Correlation between necrosis staging and hip pain grading in patients

Stage I necrosis (34.68%) and stage II necrosis (50.81%) dominated the 124 hips having pain. Among 34 hips in necrosis stage I, 10 hips (29.41%) had pain; among 59 hips at necrosis stage II, 43 hips (72.88%) had pain; among 81 hips at osteonecrosis stage III, 63 hips (77.78%) had pain; and among 17 hips at osteonecrosis stage IV, 8 hips

Table 1: Quantitative distribution of hip pain grades in various bone marrow edema grades.

Bone marrow edema	Pain grading			Total (%)
	Grade 0 (%)	Grade1 (%)	Grade 2 (%)	
Grade 0	48(92.31)	3(5.77)	1(1.92)	52(100)
Grade1	19(19.79)	57(59.38)	20(20.83)	96(100)
Grade 2	0	17(39.53)	26(60.47)	43(100)
Total	67(35.08)	77(40.31)	47(24.61)	191(100)

Table 2: Quantitative distribution of hip pain grades in various necrosis stages.

Stage of necrosis	Pain grading			Total (%)
	GGrade0 (%)	Grade1 (%)	Grade2 (%)	
I	24(70.59)	9(26.47)	1(2.94)	34(100)
II	16(27.19)	41(69.49)	2(3.39)	59(100)
III	18(22.22)	23(28.40)	40(49.38)	81(100)
IV	9(52.94)	4(23.53)	4(23.53)	17(100)
Total	67(35.08)	77(40.31)	47(24.61)	191(100)

(47.06%) had pain. Necrosis stages I ~ II were associated with hip pain grading ($P < 0.001$). Comparison of stage I with stages II and III, and comparison between stage III and stage IV all found statistically significant differences ($P < 0.05$). Rank sum test showed significant differences in hip pain grading among stages I ~ II necroses ($P < 0.001$). Moreover, with the aggravating necrosis stage, mean ranks of pain grading increased gradually, which were 57.00, 88.58 and 120.62, respectively, for stages I, II and III. Mean rank for stage III necrosis was 82.47, Table 2.

3.3 Correlation between ratio of necrotic area grading and hip pain grading in patients

Necrotic area ratio grades 0~3 were significantly correlated with hip pain grading ($P < 0.001$). Comparison of grade 0 with grades 1, 2 and 3, comparison of grade 1 with grades 2 and 3, and comparison between grade 2 and grade 3 all found statistically significant differences ($P < 0.05$). Rank sum test showed significant differences in hip pain grading among grades 0~3 ratios of necrotic area ($P < 0.001$). Moreover, with the aggravation of lesion, mean ranks of hip pain grading increased gradually, which were 36.88, 98.03, 123.87 and 151.93, respectively, for grades 0, 1, 2 and 3, Table 3.

Table 3: Quantitative distribution of hip pain grades in various ratios of necrotic area.

Ratio of necrotic area	Pain grading			Total (%)
	Grade0 (%)	Grade1 (%)	Grade2 (%)	
Grade 0	48(96.00)	2(4.00)	0	50 (100)
Grade1	10(14.93)	54(80.60)	3(4.48)	67 (100)
Grade 2	9(19.15)	14(29.79)	24(51.06)	47 (100)
Grade 3	0	7(25.93)	20(74.07)	27(100)
Total	67(35.08)	77(40.31)	47(24.61)	191(100)

4 Discussion

Previous studies [4,8-10] have found a correlation between bone marrow edema and hip pain. However, their sample sizes were all limited [11], so the specific correlations required confirmation by more clinical data. Currently, there are three methods for assessment of bone marrow edema degree, namely Sowers et al., [12] grading method based on size of bone marrow edema on MRI, Geng Xiaopeng et al., [13] grading method based on slices involved by bone marrow edema on MRI, and Zhao Peirong et al.'s [14] grading method based on edema sites on MRI. In the current study, we adopted the grading method of Zhao Peirong et al., as He Wei et al., [4] have demonstrated that it is simple and practical. In our study, mean ranks of hip pain grading in patients increase gradually with aggravating bone marrow edema, which are 40.73, 104.66 and 143.49, respectively, for grades 0, 1 and 2. Our results corroborate with those of He Wei et al., indicating that bone marrow edema is positively correlated with hip pain. Bone marrow edema means accumulation of extracellular fluids in affected bone marrows and increased intraosseous pressure [4,15]. Increase in bone marrow edema grades may lead to increased intraosseous pressure, thereby stimulating increase in the number of pain receptors in the hip, and increasing patients' pain grades.

In our study, stage I necrosis (34.68%) and stage II necrosis (50.81%) dominate the 124 hips having pain. For stages I ~ II, mean ranks of pain grading increase gradually with the aggravating necrosis stage, which were 57.00, 88.58 and 120.62, respectively, for stages II, III and IV. However, mean rank for stage III necrosis was 82.47. Stages, when arranged in an ascending order of mean ranks of pain grading, were stage I (57.00), stage II (82.47), stage III (88.58) and stage IV (120.62). Why patients in necrosis stage IV had alleviated hip pain needs further study. The reason may be because stage I INFHs

are mostly asymptomatic, most symptomatic ONFHs are already in ARCO stages II and III, while stage IV INFH patients have already been confirmed by X-ray or CT, and did not undergo MRI reexamination. Prospective studies are needed for confirmation.

The correlation between ratio of necrotic area and hip pain has never been reported in the literature. However, Zhao Fengzhao et al., have compared the values of necrotic area ratio and necrosis index in femoral head collapse, and stated after Cox hazard regression analysis that the relative risk of necrotic area ratio is 1.043 ($P = 0.000$), whereas the relative risk of necrosis index is 1.020. They claimed that the ratio of necrotic area does not vary with the prolongation of disease course [5], so we selected this area for study. We found that mean ranks of hip pain grading increased gradually with the increasing ratio of necrotic area, which were 36.88, 98.03, 123.87 and 151.93, respectively, for grades 0, 1, 2 and 3. This indicates the association between ratio of necrotic area and pain. Nevertheless, calculation of necrotic area ratio is rather complex, so if computational procedure can be developed for MRI system, it may be beneficial for clinicians to use necrotic area ratio in clinical practice.

In conclusion, we believe that the hip pain grading is positively correlated with the degree of bone marrow edema, necrosis staging and ratio of necrotic area in NONFH patients. Such correlation may be associated with intraosseous pressure and pain factors. Increase in bone marrow edema stages results in increased intraosseous pressure, thereby stimulating increase in the number of pain receptors in the hip, and increasing patients' pain grades. Increase in necrosis stages and necrotic area ratio grades may lead to increased release of pain factors, which similarly stimulates increase in the intensity of pain receptors in the hip, and increases patients' pain grades as well. The specific reasons need confirmation by further studies. Ratio of necrotic area has a more close relationship to pain. Understanding of such relationship is beneficial for clinicians to comprehensively predict the femoral head bone marrow edema, necrosis stage and necrotic area ratio based on the degree of hip pain in patients. In the treatment of hip pain in NONFH patients, simultaneous use of core decompression and blood circulation-activating & stasis-removing TCM drugs for reducing intrafemoral pressure combined with anti-inflammatory & analgesic drugs such as NASIDs may offer better results.

Conflict of interest statement: Authors state no conflict of interest.

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