Research Paper

Effects of Core Decompression and Local Deferoxamine Injection on Clinical Outcomes and Revascularization of Lunate Carpal Bone in Kienböck Disease: A Pilot Study

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ABSTRACT

Background: Avascular necrosis of the lunate or Kienböck disease is a rare disorder with unknown etiology and challenging treatment.

Objectives: In this study, we evaluated the effects of local deferoxamine injection as an angiogenic molecule and core decompression to treat Kienböck disease.

Methods: In a pilot clinical trial, 8 patients with stage I to IIIA of Kienböck disease were treated with core decompression and local deferoxamine injection (0.5 mL 500 mg/mL). The outcome measures included wrist range of motions, pinch and grip strength, patient-rated wrist/hand evaluation (PRWE), a short form of disabilities of the arm, shoulder, and hand (Quick-DASH), and visual analog scale (VAS) for pain. The assessment of lunate revascularization was also done by T1- and T2-weighted magnetic resonance imaging. All measurements were done before the intervention and 3, 6, and 12 months after the intervention.

Results: Wrist flexion, extension, ulnar and radial deviation, and pinch and grip strength were continuously improved over the postoperative periods. These improvements were statistically significant. The mean final pinch and grip strength averaged 87.4% and 72.8% of the non-involved hand, respectively. PRWE, Quick-DASH, and VAS scores were also continuously and significantly improved over the study period. The lunate vascularization revealed a continuous improvement in 6(75%) patients.

Conclusion: Local deferoxamine injection in addition to core decompression could improve the radiologic and clinical outcomes of patients suffering from Kienböck disease.

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1. Introduction

Kienböck disease is a rare and debilitating condition caused by avascular necrosis of the lunate [1-3]. The exact etiology of Kienböck disease is not understood. However, several causative factors, including a shortened ulna, lower number of arteries, type I lunate morphology, and reduced radial inclination angle have been suggested as the intrinsic risk factors of Kienböck disease [4, 5]. Meanwhile, repetitive microtrauma has been noticed as the major extrinsic risk factor for this disorder [4, 6].

Kienböck disease is often a progressive disorder and results in joint deterioration within 3 to 5 years if left untreated [7]. Even so, there is no consensus about the optimal treatment approach for this disease. Radial shortening osteotomy is one of the most preferred methods to treat Kienböck disease. Although it has been repeatedly reported as a reliable method to treat Kienböck's disease, the disease symptoms remain unresolved in a considerable number of patients [8, 9]. In addition, non-union is considered a serious complication of radial shortening osteotomy [10]. Therefore, there are attempts to develop more efficient treatment methods for Kienböck disease.

Traditionally, core decompression in the early stages of Kienböck disease has been shown to improve blood supply to the lunate through the reduction of intraosseous pressure in the affected area [11, 12]. Recently, direct revascularization of the lunate using vascularized bone grafting, mesenchymal stromal cells, and administration of angiogenesis factors, such as bone morphologic proteins has attracted more attention [13-15].

Novel studies have suggested that the hypoxia-inducible factors (HIFs) and their target gene vascular endothelial growth factor (VEGF) are particularly involved in the angiogenesis [16]. Deferoxamine is an iron chelator that has been demonstrated to inhibit the degradation of HIF-1α, thereby increasing the expression of HIFs target genes, and leading to improved vascularization [17]. In this respect, the local administration of deferoxamine in the steroid-induced osteonecrosis of rabbit femoral heads has improved angiogenesis and bone repair [18]. However, the effects of local deferoxamine administration on improving lunate osteonecrosis have not been investigated in previous studies.

Objectives

We hypothesize that a combination of direct and indirect induction of angiogenesis, using the local administration of deferoxamine and core decompression, respectively, might result in improved angiogenesis of the lunate. In this pilot study, we tested this hypothesis in a series of 8 patients with stage I to IIIA Kienböck disease.

2. Methods

This clinical trial study was approved by the Institutional Review Board of our institute under the code IR.IUMS.FMD.REC.1397.217. The study protocol was also registered in the Iranian Registry of Clinical Trials (IRCT) under the code IRCT2017073035382N1. A written informed consent form was obtained from all patients to use their medical data for publication, including any necessary photographs. In a pilot study, 8 patients with type I-IIIA Kienböck disease, according to Lichtman's modification of the Stahl classification [19], were treated by core decompression combined with the local administration of deferoxamine. The inclusion criteria were being in the age range of 18 to 60 years and having no comorbid chronic underlying disease, such as rheumatologic disease, collagen vascular disease, chronic heart failure, renal failure, and so on. Patients with a history of treatment for Kienböck disease, as well as patients who were under corticosteroids or immunosuppressive medications were excluded from the study. In addition, patients with a history of fracture or infection in the same wrist were excluded.

The diagnosis of Kienböck disease was based on the classic approach and according to the patient's complaint, physical examination, plain anteroposterior, and lateral radiographs. In all cases, the diagnosis was confirmed by wrist T1- and T2-weighted magnetic resonance imaging (MRI). After diagnosis, we discussed the situation with our patients. The theories on the etiology and treatment options, as well as the details of the current trial, were described to them. For patients who declined to participate in the study, a classic treatment, including radial shortening or capitate carpal bone shortening was implicated based on the stage of their disease and ulnar variance.

Demographic characteristics of patients

A total of 8 patients with stage I-IIIA Kienböck disease were included in this study. The study population consisted of 4(50%) males and 4(50%) females with a mean age of 33.6±12.9 years(range 20 - 62). The disease was at stage I in 3(37.5%), stage II in 3(37.5%), and stage IIIA in 2(25%) patients. A history of trauma was noticed in 3(37.5%) patients. In 3(37.5%) patients, the disease was in the dominant hand, while in the remaining

5(62.5%) patients, the disease was in the non-dominant hand. The demographic and clinical characteristics of the patients are provided in Table 1.

Surgical technique

After the preoperative administration of antibiotics (cefazolin 1 g, EXIR Pharmaceutical Co, Borujerd, Iran) and routine surgical skin preparation and draping on the radiolucent arm board and under the control of a pneumatic tourniquet, we used C-arm to localize the lunate carpal bone (Figure 1A). Before starting the surgeries, we designed and made a small aluminum plate in such a way that three 2 mm holes in its center could be located exactly on the lunate bone (Figure 1B). Then a 2-cm of longitudinal dorsal incision was made over the lunate (Figure 1C). After relocating the extensor tendons radial or the ulnar side, the handmade aluminum indicator was fixed to the area using 1.5 mm Kirshner Wires (KWs) (Figure 1D). Then we inserted 3 KWs through the central holes in the lunate and drilled the lunate using a cannulated 2 mm drill bit to produce a tunnel of 10 mm length (Figure 1E). We did not open the wrist joint capsule during the procedure.

Since no similar human study was available, the dose of deferoxamine was extracted from previous animal studies [20, 21]. Accordingly, a dose of 200 µmol was selected, which according to the molecular weight of deferoxamine (560.693 g/mol), this dose was equivalent to approximately 112 mg of deferoxamine. On the other hand, because the volume of the canals was about half of a cm3, one ampoule of 500 mg deferoxamine(Desferal, Novartis Pharma Stein AG Stein, Switzerland) was dissolved in 4 mL of sterile distilled water. Then, 0.5 mL of this solution was injected into the created canals.

After repairing the retinaculum and skin, we applied an external fixator by inserting its distal Schanz pins in the second metacarpal bone and proximal ones on the distal radius in a small amount of traction which created a 2 mm distance in the radiocarpal joint to unload the lunate bone (Figure 1F). The external fixator was removed after 6 weeks, and the patient was referred to the physiotherapy unit to overcome the wrist stiffness.

Outcome measures

The objective outcome measures included passive range of motion (ROM) of both wrists in flexion, extension, ulnar, and radial deviation, as well as pinch and grip strength of both hands. ROM was measured using a goniometer and recorded by the hand therapist who was blind to the study protocol. The pinch and grip strength of both hands were assessed and recorded by the same person using a pinch gauge (Hydraulic Pinch Gauge SH5005, Saehan Corporation, Masan, Korea), and a dynamometer (Hydraulic Hand Dynamometer SH5001, Saehan Corporation, Masan, Korea), respectively. Subjective measures of the outcome included the evaluation of the wrist function using a validated form of patient-rated wrist/hand evaluation (PRWE) [22] and the short form of disabilities of the arm, shoulder, and hand (Quick-DASH) [23] questionnaire, in addition to pain evaluation using the visual analog scale (VAS) scoring system on a scale of 0–10 (0: no paint; 10: worst pain). In all subjective measures, a higher score was indicative of more disability.

Objective and subjective outcome measures were assessed before the surgery and 3, 6, and 12 months after the surgery.

Table 1. Demographic and clinical characteristics of patients with kienböck disease treated with core decompression and local deferoxamine injection

ID	Age (y)	Gender	Disease Laterality	Hand Dominancy	History of Trauma	Stage
1	25	Female	Right	Right	No	IIIA
2	20	Male	Left	Right	No	IIIA
3	36	Female	Left	Right	No	II
4	33	Male	Left	Right	No	II
5	38	Female	Left	Left	Yes	II
6	62	Female	Left	Right	No	I
7	28	Male	Right	Right	Yes	I
8	27	Male	Right	Left	Yes	I

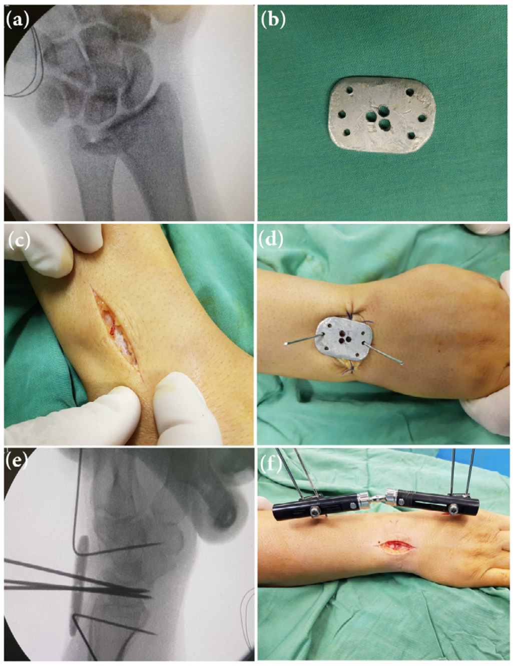

Figure 1. Process of deferoxamine injection into the lunate

A: Localizing the lunate carpal bone under the C-arm; B: Designing an aluminum plate; C: Making a longitudinal dorsal incision over the lunate; D: Fixing the aluminum plate using Kirshner wires; E: insertion of 3 Kirshner wires through the central holes of the plate and drilling the lunate to produce a tunnel 10 mm in length for the injection of deferoxamine.

The radiographic evaluation included standard recommended anteroposterior and lateral radiographs [24]. T1- and T2-weighted 1.5 Tesla MRI was used to evaluate the vascularity of the lunate 3, 6, and 12 months after the operation. For 1 patient (case 6), the postoperative MRI was only performed once (12 months after the surgery) because of the patient's claustrophobia. Two radiologists who were blind to the study evaluated the MRI images' sequences to assess the lunate bone's vascularity status.

Statistical analysis

The prevalence of Kienböck disease was reported at 0.27% in the study by Leeuwen et al. [25]. Using this prevalence, the absolute error of 0.05 and type 1 error of 5%, a number of 6 patients with Kienböck disease were identified sufficient for this pilot study.

The statistical analysis was performed by the SPSS software, version 16, for Windows operating system. The descriptive data were provided as a Mean±Standard Deviation (SD) of number and percentage. A Friedman test was used to compare the mean difference of the outcome measures over the study periods. The P value of less than 0.05 was considered significant.

3. Results

Passive range of motion

The mean radial deviation of the involved hand was 6.9º±5.9º before the surgery, 11.3º±4.4º three months after the surgery, 13.75º±3.5º six months after the surgery, and 16.9º±5.3º one year after the surgery. The mean difference in radial deviation over the study periods was statistically significant (P<0.001) (Figure 2A).

The mean ulnar deviation of the involved hand was 11.3º±9.9º before the surgery, 13.8º±8.8º three months after the surgery, 16.3º±6.9º six months after the surgery, and 19.4º±6.8º one year after the surgery. The mean difference in ulnar deviation over the study periods was statistically significant (P=0.001) (Figure 2B).

The mean wrist extension of the involved hand was 30º±17.3º before the surgery, 42.5º±13.9º three months after the surgery, 53.1º±13.3º six months after the surgery, and 63.8º±10.6º one year after the surgery. The mean difference in wrist extension over the study periods was statistically significant (P<0.001) (Figure 2C).

Table 2. Passive range of motion of the involved (pre and postoperative) and non-involved hand of patients with kienböck disease treated with core decompression and local deferoxamine injection

Variables		1	2	3	4	5	6	7	8
Radial deviation(º)	Preoperative	5	10	0	5	5	20	5	5
	Postoperative (month 3)	10	15	5	10	10	20	10	10
	Postoperative (month 6)	10	15	10	15	15	20	10	15
	Postoperative (month 12)	10	20	10	15	25	20	15	20
	Non-involved hand	15	30	20	20	15	20	15	20
Ulna deviation(º)	Preoperative	5	20	0	5	15	30	10	5
	Postoperative (month 3)	5	20	5	10	20	30	10	10
	Postoperative (month 6)	10	20	10	10	20	30	15	15
	Postoperative (month 12)	10	20	15	15	25	30	15	25
	Non-involved hand	15	30	30	30	35	30	20	20
Wrist extension(º)	Preoperative	5	30	30	5	45	50	45	30
	Postoperative (month 3)	30	40	40	20	60	60	50	40
	Postoperative (month 6)	40	50	50	30	65	70	60	60
	Postoperative (month 12)	60	70	60	40	70	70	70	70
	Non-involved hand	60	70	80	70	70	80	70	80
Wrist flexion(º)	Preoperative	45	10	0	5	70	65	30	10
	Postoperative (month 3)	50	40	30	20	70	70	50	15
	Postoperative (month 6)	60	60	40	30	75	70	70	20
	Postoperative (month 12)	70	75	50	45	82	70	80	25
	Non-involved hand	80	80	80	80	80	90	90	80
Pinch strength(lbs)	Preoperative	12	12	11	9	15	11	15	20
	Postoperative (month 3)	14	15	11	15	20	12	22	20
	Postoperative (month 6)	15	17	12	20	22	12	25	21
	Postoperative (month 12)	16	20	12	25	24	13	27	22
	Non-involved hand	17	20	20	30	24	17	28	26
Grip strength(lbs)	Preoperative	20	30	20	25	90	40	80	60
	Postoperative (month 3)	20	50	22	40	90	40	90	60
	Postoperative (month 6)	25	60	23	50	95	40	100	60
	Postoperative (month 12)	25	70	25	60	100	40	115	60
	Non-involved hand	50	70	60	105	100	65	115	115
PRWE	Preoperative	42.5	64	85	91	33	63.5	63.5	64.5
	Postoperative (month 3)	39.5	47	52.6	82	25.1	44.1	50.2	58.7
	Postoperative (month 6)	37.2	31.8	36.2	76.3	15.6	27.5	25.6	50.4
	Postoperative (month 12)	34.5	18	23	73	10	17.1	13.3	46
Quick-DASH	Preoperative	45	52	84	77	23	23	52	34
	Postoperative (month 3)	40	39	63	68	16	18	38	30
	Postoperative (month 6)	34	28	42	58	11	12	21	26
	Postoperative (month 12)	30	20	34	52	5	9	10	20
VAS for pain	Preoperative	5	7	8	6	6	5	6	9
	Postoperative (month 3)	4	5	6	5	4	4	4	6
	Postoperative (month 6)	3	3	4	3	2	3	3	5
	Postoperative (month 12)	2	1	2	2	0	3	2	3

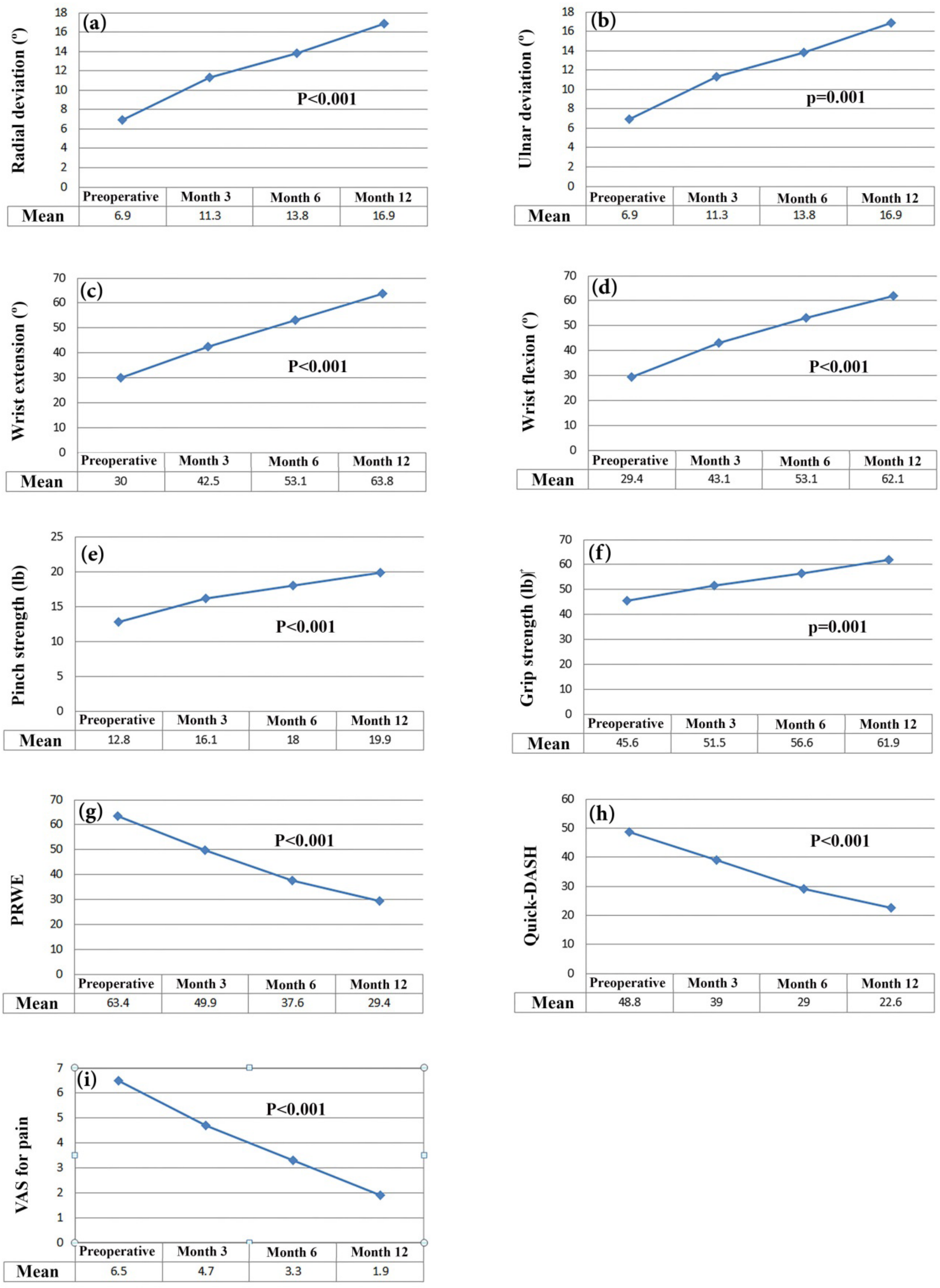

Figure 2. Comparison of mean change of outcome measures over the study periods

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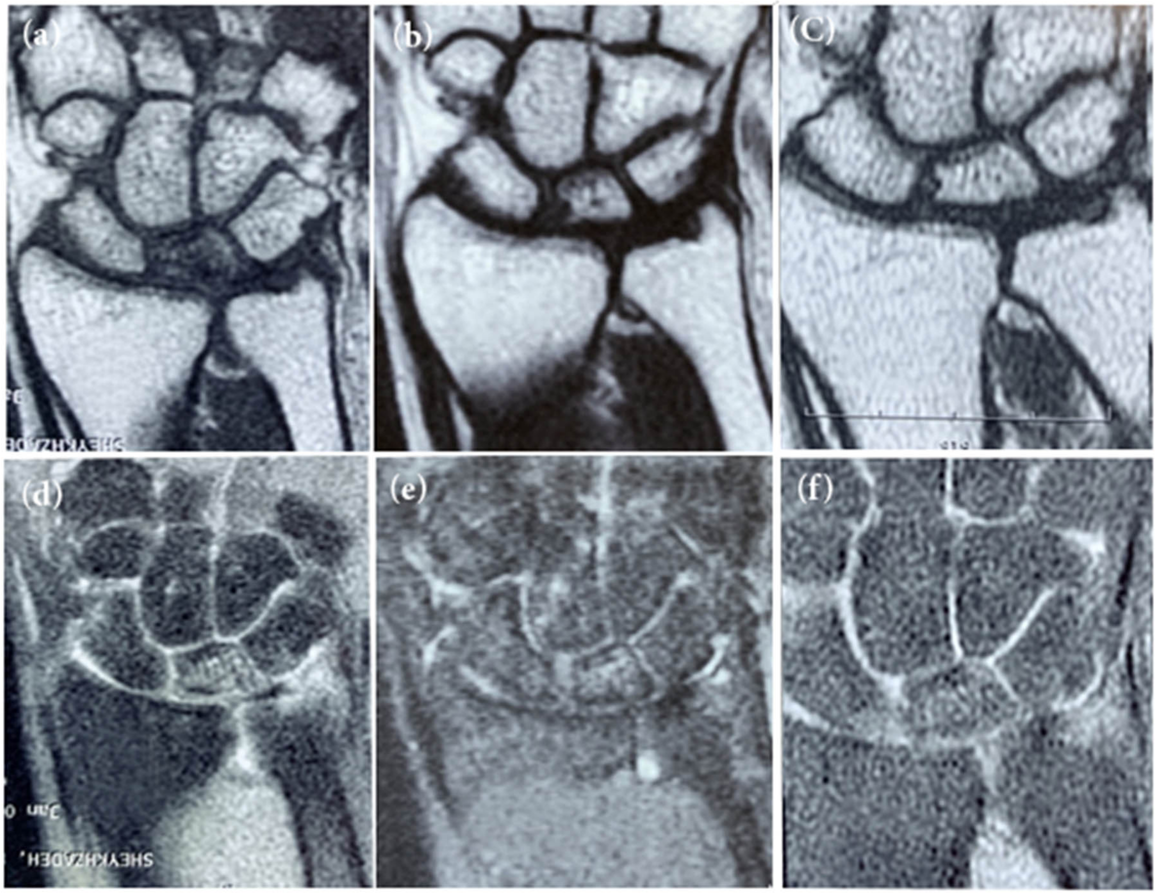

Figure 3. Comparison of preoperative and postoperative mris showing continues improvement of lunate revascularization

A: T1-weighted MRI before the surgery; B: T1-weighted MRI 6 months after the surgery; C: T1-weighted MRI 12 months after the surgery; D: T2-weighted MRI before the surgery; E: T2-weighted MRI 6months after the surgery; F: T2-weighted MRI 12 months after the surgery.

MRI: Magnetic Resonance Imaging.

The mean wrist flexion of the involved hand was 29.4º±27.7º (range 0-70) before the surgery, 43.1º±20.8º three months after the surgery, 53.1º±20.5º six months after the surgery, and 62.1º±20º one year after the surgery. The mean difference in wrist flexion over the study periods was statistically significant (P<0.001) (Figure 2D).

The mean final radial deviation of the involved hand averaged 87.1% of the non-involved hand. The mean final ulnar deviation of the involved hand averaged 73.8% of the non-involved hand. The mean final wrist extension of the involved hand averaged 88% of the non-involved hand. The mean final wrist flexion of the involved hand averaged 75% of the non-involved hand. The detailed ROMs of the involved(pre and postoperative) and non-involved hand are provided in Table 2.

Grip and pinch strength

The mean pinch strength of the involved hand was 12.7±3.4 lbs before the surgery, 16.1±4 lbs three months after the surgery, 18±4.7 lbs six months after the surgery, and 19.9±5.7 lbs one year after the surgery. The mean difference in pinch strength over the study periods was statistically significant (P<0.001) (Figure 2E).

The mean grip strength of the involved hand was 45.6±27.7 lbs before the surgery, 51.5±27.2 lbs three months after the surgery, 56.6±28.9 six months after the surgery, and 61.9±32.8 lbs one year after the surgery. The mean difference in grip strength over the study periods was statistically significant (P=0.001) (Figure 2F).

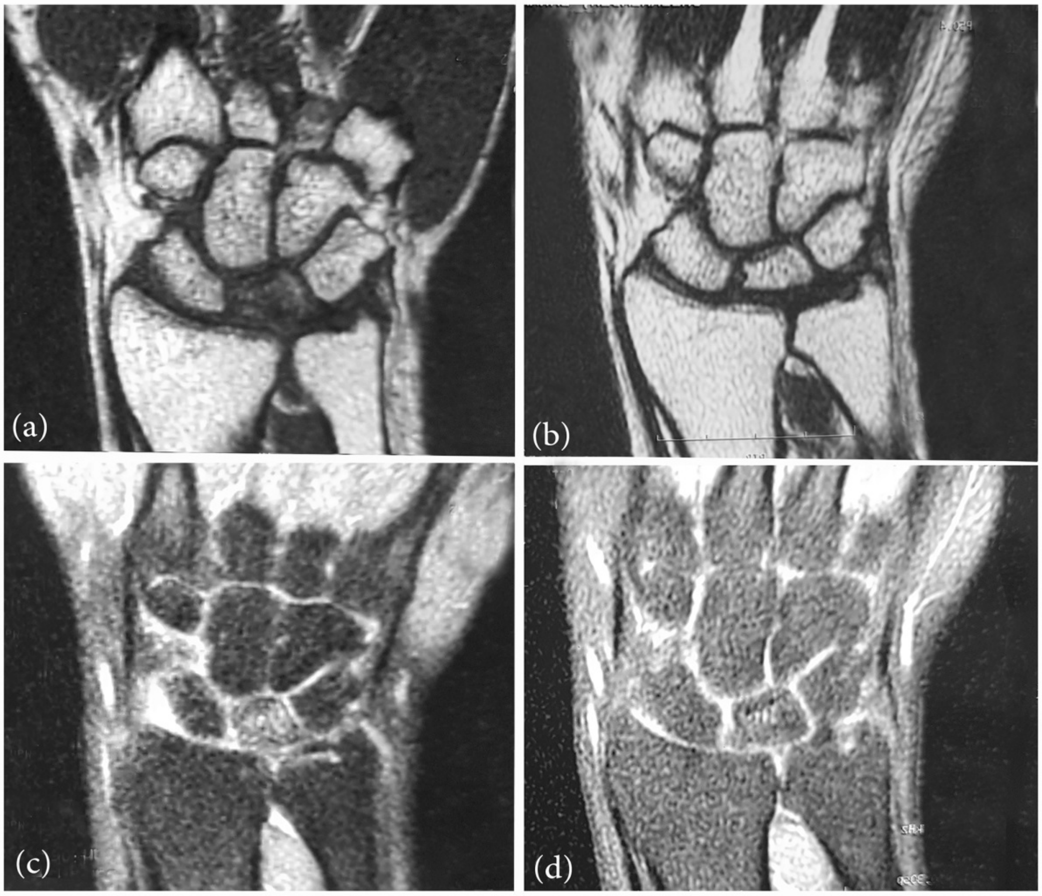

Figure 4. Almost Normal Lunate Vascularization After Treatment by Core Decompression and Local Deferoxamine Injection

A: T1-weighted MRI before the surgery; B: T1-weighted MRI 12 months after the surgery; C: T2-weighted MRI before the surgery; D: T2-weighted MRI 12 months after the surgery.

MRI: Magnetic Resonance Imaging

The mean pinch strength of the involved hand at the final follow-up averaged 87.4% of the non-involved hand. The mean grip strength of the involved hand at the final follow-up averaged 72.8% of the non-involved hand. The detailed pinch and grip strength of the involved (pre and postoperative) and non-involved hand are provided in Table 2.

Subjective evaluations

The Mean±SD PEWE score of the involved hand was 63.4±19.2 before the surgery, 49.9±16.4 three months after the surgery, 37.6±18.6 six months after the surgery, and 29.3±21.2 one year after the surgery. The mean difference in PEWE score over the study periods was statistically significant (P<0.001) (Figure 2G).

The mean Quick-DASH score of the involved hand was 48.8±22.7 before the surgery, 39±17.8 three months after the surgery, 29±15.7 six months after the surgery, and 22.5±15.6 one year after the surgery. The mean difference in the Quick-DASH score over the study periods was statistically significant (P<0.001) (Figure 2H).

The mean VAS for the pain of the involved hand was 6.5±1.4 before the surgery, 4.7±0.9 three months after the surgery, 3.3±0.9 six months after the surgery, and 1.9±1 one year after the surgery. The mean difference of VAS for pain over the study periods was statistically significant (P<0.001) (Figure 2I). The detailed pre and postoperative subjective measures are provided in Table 2.

Evaluation of vascularization changes of lunate

After comparing the preoperative and postoperative MRIs of the lunate, the lunate vascularization was improved in 6(75%) patients (Figure 3). In one patient, the lunate vascularization turned in almost normal at the final follow-up (Figure 4).

Postoperative complications

No postoperative complications, such as wound or pin site infections occurred in the patients.

4. Discussion

Treating hand disorders could be challenging, and efforts continue to identify more effective therapeutic approaches for these conditions [26, 27]. Similarly, treating Kienböck disease is challenging. This study evaluated the effects of core decompression adjunct with local deferoxamine injection in treating Kienböck disease at stages I-IIIA. According to our results, this approach significantly improved the objective measures of the outcomes, including wrist ROM, pinch, and grip strength. The subjective measures of the outcomes, including PRWE and Quick-DASH scores were significantly improved, as well. In addition, the improvement of lunate revascularization was obvious in the MRI of the majority of cases.

Lunate revascularization in Kienböck disease has been the subject of several investigations. The majority of these studies have focused on the indirect revascularization of the lunate through the induction of new bone formation. Capitate shortening and radial shortening osteotomies are considered the most successful indirect methods to provide lunate revascularization [28, 29]. Core decompression efficacy has been less investigated as an indirect approach for the revascularization of the lunate. Mehrpour et al. examined the efficacy of lunate core decompression in treating 20 patients with stage I to IIIB Kienböck disease. After the surgery, meaningful improvements were observed in the ROM of 18 patients. They suggested lunate core decompression as a simple and effective surgical procedure in the treatment of Kienböck disease [30]. The efficacy of core decompression in the treatment of this disorder has also been demonstrated in other studies [31, 32].

Several procedures have also been proposed for the direct revascularization of the lunate, which are generally used in combination with the indirect revascularization methods. Among them, vascularized bone graft (VBG) is considered the most widely investigated method [33]. Therefore, attempts continued to develop more efficient lunate direct revascularization techniques. Recently, stem cell injection along with core decompression has been suggested as a new treatment modality for Kienböck disease with synergistic revascularization effects with low potential complications [13, 34, 35].

The role of deferoxamine as an angiogenic molecule has been evaluated in the induction of bone revascularization in several disorders. Donney et al. used deferoxamine to increase the vascular volume beyond the normal response in mandibular distraction osteogenesis. In their results, they reported a 40% increase in the number of vessels, which was readily observed with micro-computed tomography image reconstruction [36]. In another study, Donneys et al. evaluated the efficacy of local deferoxamine injection to augment vascularity and improve bony union in the healing of pathologic fracture after radiotherapy. According to their in vitro evaluations by endothelial tubule formation assays, deferoxamine reduced the detrimental effects of radiation on angiogenesis. According to their in vivo study, animals with la eft mandibular fracture who received a human equivalent dose of radiotherapy demonstrated almost 75% diminished incidence of associated non-unions. They suggested localized deferoxamine injections to subside the severe vascular diminution caused by radiotherapy [20]. The same results were reported in the animal study of Farberg et al. [21]. Meanwhile, Stewart et al. evaluated the effect of local deferoxamine loaded on the cylindrical manufactured scaffold on vascularity and healing of a segmental defect of the rat femur. Their results revealed increased vascularity and bone bridging, as well as improved stiffness after 6 weeks [37].

To the best of our knowledge, this is the first study to evaluate the role of local deferoxamine injection in the improvement of lunate vascularization in Kienböck disease. In line with the results of earlier investigations, the radiologic assessments of the present study revealed the positive impact of local deferoxamine injection on lunate revascularization. This positive effect was associated with the significant improvement of objective and subjective outcome measures.

This study was not without limitations. The main limitation of the study was the small number of patients. The absence of a control group of patients treated by core decompression alone could be regarded as another limitation of the study. Also, we did not use a scaffold or frequent injection for deferoxamine administration. Therefore, future controlled studies with larger study populations and better designs are required to confirm the results of the present study.

5. Conclusions

The addition of local deferoxamine injection to core decompression could improve the radiologic and clinical outcomes of patients with Kienböck disease. However, the limitations of this study, particularly the lack of a control group, do not allow a definitive conclusion, and future complementary studies are required to confirm the present results.

Ethical Considerations

Compliance with ethical guidelines

This clinical trial study was approved by the Institutional Review Board (Code IR.IUMS.FMD.REC.1397.217). The study protocol was also registered in the Iranian Registry of Clinical Trials (IRCT) (Code IRCT2017073035382N1). A written informed consent form was obtained from all patients to use their medical data for publication, including any necessary photographs.

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Authors' contributions

Conceptualization: Farid Najd Mazhar and Ali Mohammad Sharifi; Methodology: Mojtaba Maztarzadeh; writing the original draft: Alireza Mirzaei.

Conflict of interest

The authors declared no conflict of interest.

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