Case Report

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# Mesenchymal Stem Cell Injection into Kidney Acupoints: A Case Report of A Feline With Chronic Kidney Disease

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**ABSTRACT**

**Abbreviations:** CKD: Chronic Kidney Disease; TCM: Traditional Chinese Medicine; IV: Intravenous

## Introduction

The kidneys play an important role in maintaining homeostasis in the organism by filtering and excreting metabolic waste products [1]. Kidney disease is common in small animals and is characterized by the loss of functionality of one or both of the kidneys. This can be primary, with the nephrons degrading over time, or secondary, caused by a deleterious agent [2]. Chronic Kidney Disease (CKD) occurs when renal dysfunction persists for at least 3 months and is generally characterized as a progressive and irreversible disease that leads to reduction in mass and eventual failure of the kidneys [3]. Affected animals may present with the following symptoms: weight loss, loss of appetite, vomiting, polyuria, polydipsia and uremic fetor [3]. Due to the progressive and irreversible character of CKD, new therapeutic approaches are being evaluated in an attempt to further improve quality of life for patients and perhaps discover a cure. One of these treatments is cellular therapy with mesenchymal stem cells [4]. MSCs are adherent, fibroblast-like cells that are able to differentiate into diverse cellular lineages and that, in certain microenvironments, can be induced to differentiate into specific lineages [5]. MSCs have been reported to have therapeutic potential in the treatment of kidney disease, especially due to their abilities to promote reno-protective effects, induce proliferation, promote angiogenesis at the affected location, inhibit the inflammatory response, and improve renal function [6,7].

In several studies, MSC treatment has been shown to significantly improve quality of life [8], and is specifically correlated to weight gain, increased appetite, and increased activity levels in CKD patients [9]. Another study has confirmed the safety of allogenic cell applications and observed a reduction in vomiting frequency associated with MSC therapy [10]. A range of MSC dosages for chronic kidney disease treatment have also been tested, and it has been demonstrated that intravenous application of smaller doses causes a small reduction in serum creatinine in cats, whereas higher doses caused a high incidence of adverse effects [10]. Conventional treatment of CKD is based on fluid therapy, nutrition, and dialysis in order to promote a higher quality of life for the animal [11]. Additionally, Traditional Chinese Medicine (TCM), known for its focus on maintaining homeostasis [12], has been used to ameliorate quality of life in CKD patients as a complementary therapy [13]. Acupuncture, a TCM technique, is based on the insertion of needles into dermal and subcutaneous tissue at specific points, termed acupoints, in a non-harmful way, with the goal of guaranteeing homeostatic equilibrium and achieving desired therapeutic effects [14].

Acupoint injection is a modification of this technique and enables the subcutaneous application of therapeutic drugs at an acupoint by exchanging the typical acupuncture needle for a syringe needle. This technique has a long history, and recent research has confirmed its efficacy and quick onset of symptom relief. Pharmaceutical agents injected at acupoints provide the double benefit of prolonged stimulation of the acupoint and prolonged absorption of the pharmaceutical agent, two benefits that intravenous injection lacks [15]. Mesenchymal stem cells, which achieve their therapeutic effects through paracrine activity and have the potential to remain active in the patient's organism, continuously secreting bioactive factors, for weeks or months after injection, avail themselves as excellent candidates for this technique. As MSCs possess paracrine activity that can improve kidney function, extending their activity in situ should translate to an augmented therapeutic effect when compared to other application routes. In fact, a previous study was able to successfully treat hip dysplasia in dogs by injecting MSCs at acupoints [16], and a number of studies have demonstrated the efficacy of acupoint injection in treating CKD [17-19]. Considering these studies as a whole, we may conclude that there is not yet sufficient data available regarding stem cell applications for the treatment of CKD in dogs and cats to draw strong conclusions regarding predictable patient responses and outcomes or best clinical practices. However, the studies that have been performed using MSCs or TCM techniques have been able to achieve positive outcomes in CKD patients. The objective of this case report is to describe the combination of these beneficial techniques as a supplemental therapy in the treatment of a feline CKD patient.

## Case Report

For the present work, a patient of the species Felis catus from a private clinic in Sao Paulo State, Brazil, was selected for the study. The patient was 2 years old at the time of the study and was diagnosed with CKD at 9 months old. The veterinarian Denise de Fatima Rodrigues applied the cells and evaluated the patient during the study period. Consent had been previously obtained from the owners for the carrying out of the treatment and observation during the study. MSCs were provided by CellTech - Stem Cell Technologies LTDA, and 1 x $10^6$ cells per kilogram of body mass were injected subcutaneously at the acupoints VB25, B23, and B52 bilaterally, as well as the VC3 point unilaterally, all of which are kidney acupoints. Table 1. On the day of the cell therapy application, the animal was submitted to a kidney function blood exam and a hemogram. The second cell application was performed 21 days after the first, and the third application was performed 28 days after the second. In order to track the patient's response, a new hemogram, the results of which can be observed in Table 1, was performed 25 days after the third application. Prior to cellular therapy, the animal presented daily vomiting in large quantities and a lack of appetite, and the patient was receiving fluid therapy three times per week. After the applications the patient reduced the frequency of fluid therapy to twice per week. Additionally, higher levels of activity, absence of vomiting, normal appetite and urine output, and an increase of 1.1 kg in weight were reported by the owner and confirmed by the veterinarian.

**Table 1:** Table 1- Patient Clinical Data.

| Animal | At 1st cell application (reference range) | 25 days after 3rd application (reference range) |
|---|---|---|
| Feline, 2 years old, undergoing fluid therapy and taking prokidney (a homeopathic medicine) three times per week | **Creatinine:** 2.2 mg/dl (0.8 to 1.6 mg/dl) **Urea:** 75 mg/dl (10 to 56 mg/dl) | **Creatinine:** 1.9 mg/dl (0.8 to 1.6 mg/dl) Urea: 64 (10 to 56 mg/dl) |
| | **Weight:** 3.3 kg **Symptoms:** daily intense vomiting and lack of appetite | **Weight:** 4.4 kg **Symptoms:** lack of vomiting, normal appetite and normal urine volume |

## Discussion

In the bibliography researched for this case study, no cases of CKD treatment with MSCs using acupoints were found, only Intravenous (IV) administrations. Although cell delivery is typically performed intravenously for CKD patients, intravenous application reduces to a questionable level the quantity of cells that reach the injury site. This phenomenon has been attributed to the fact that the cells first pass through the lungs, causing the majority of the cells to initially become trapped there [20]. It has also been reported that cells administered by intravenous infusion could

not be detected in the organism a few days after administration, while subcutaneously administered cells could be detected for 3 to 4 weeks, and intramuscularly administered cells for more than 5 months. Moreover, a study analyzing the biodistribution and retention of MSCs administered locally via intramuscular injection in mice observed that the cells were detectable for 3 months after the injection, though only at the injection sites. Interestingly, despite the fact that the cells did not distribute themselves throughout the body, they were able to reduce inflammation in distant areas of the organism, which can be explained by the fact that the therapeutic effects of the cells are related to their paracrine activity. All these facts together explain the rationale underlying the decision to inject the cells subcutaneously into acupoints. Due to the fact that the subcutaneous route has elicited good results, allowing for detection of MSCs up to 3 or 4 weeks later, the applications in this study were performed on acupoints at an interval of 28 days between applications.

## Conclusion

The results of the experiment support the hypothesis that subcutaneous cell therapy at the acupoints described corroborated in the reduction of vomiting, normalization of urine output, appetite, and activity levels, and weight gain. Creatinine and urea levels were also found to be lower at the final exam, however, to better understand the interaction of subcutaneous MSC therapy at acupoints in CKD patients, including the symptomatology and results of biochemical exams, it would be necessary to perform tests on a higher sample size of animals for a longer period of time.

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