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Evaluation of the Role of Adipose-Derived Stem Cells in the Healing of Indomethacin-Induced Gastric Ulceration in Rats

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Abstract

Purpose: To study the effect adipose derived stem cells (ADSCs) in a rat model of gastric ulceration.

Methods: 72 albino rats divided into 3 groups: Group N (Negative control), Group D (positive control); and Group T (ADSCs treated group). Six animals of each group were sacrificed 1, 3, 4 and 5 days after ulcer induction. Each stomach was extracted for macroscopical and histopathological assessment. Vascular endothelial growth factor (VEGF), Prostaglandin E_2 (PGE_2) and polymerase chain reaction (PCR) for human alu sequences in gastric tissue homogenate were done.

Results: ADSCs transplantation improved the histopathology of the gastric tissue in stem cell treated group. Also the result of ulcer index was significantly decreased in stem cell treated group at day 3, 4 and 5 of the study comparing with the indomethacin challenged group. Regarding ELISA results, ADSCs restored the levels of PGE_2 to the normal levels and increased the VEGF levels significantly to above normal levels. PCR revealed that stem cells successfully engulfed into the gastric wall by the third day and continued to persist until the 5th day.

Conclusion: Homing of stem cells, release of growth factors that induce angiogenesis like VEGF and other substances as PGE_2 may be the underlying mechanisms of the improved gastric ulceration healing.

Keywords: Adipose-derived stem cells; Gastric ulcer; Rats; PGE_2; VEGF; Indomethacin

Introduction

Gastric ulcer is a major health hazard in terms of both morbidity and mortality [1]. Inadequate dietary habits, cigarette smoking, excessive ingestion of non-steroidal anti-inflammatory agents, stress, hereditary predisposition and infection by Helicobacter pylori may be responsible for the development of peptic ulcer [2]. Indomethacin is a commonly used type of NSAIDs that induces ulceration of stomach and small intestine both in experimental animals and humans [3]. Several products have been employed for the treatment of gastroduodenal ulcer and peptic diseases, but they are not completely effective and produce many adverse effects [2] such as arrhythmias, impotence, gynaecomastia and hematopoietic changes [4]. The interest in the stem cell-based therapies for gastrointestinal injury has been growing recently. Chang et al. showed that autologous intravenous BMMSCs transplantation can accelerate gastric ulcer healing in injured gastric mucosa in a rodent model [5]. Fat obtained from humans is a rich source of MSCs also known as adipose-derived stem cells (ADSCs) which have the ability to generate several types of tissues (plasticity) [6]. ADSCs are suitable for treatment of wounds because of their potential to differentiate into several cell types, such as endothelial cells and secrete angiogenic and anti-apoptotic factors [7]. They can accelerate regeneration of injured regions in experimental colitis through production of hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF) and adiponectin [8]. The secretion of VEGF by ADSCs under normal and abnormal conditions (i.e. hypoxia) has been reported as the factor underlying ADSC-mediated angiogenesis [9]. In this study we investigated the effect and mechanism of intravenous transplantation of human adipose derived stem cells (ADSCs) on the healing of gastric ulcers induced by indomethacin in rats.

Material and Methods

Animals

A total of seventy two adult albino Westar female rats weighing 250 gm ± 50 gm were used. Rats were purchased from the Ophthalmology Research Institute (Giza, Egypt); housed in clean cages under hygienic conditions and allowed to acclimatize for seven days before starting the experiment. Rats were kept on a standard chow and water ad libitum then they were fasted for 24 h prior to the experiment but allowed free access to water. All experimental protocols were approved by the Institutional Animal Care and Use Committee at Suez Canal University. All efforts were made to minimize animal suffering and to reduce the number of animals used. The "Principles of laboratory animal care" were followed, as well as specific national laws where applicable.

Experimental protocol

Rats were randomly allocated into three groups, 24 rats each

- Group N (Negative control - untreated group): normal rats weren't subjected to either gastric ulcer or stem cell treatment.
- Group D (positive control- Indomethacin-induced gastric ulcer group): rats were subjected to gastric ulceration then received phosphate buffer saline vehicle.
- Group T (ADSCs treated group): rats were subjected to gastric ulceration then received intravenous injection of (3×10^6) ADSCs/rat via tail vein.

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Animals were anesthetized with ketamine 50 mg/kg intraperitoneally and sacrificed after 1 day, 3 days, 4 days and 5 days after ulcer induction (6 animals in each experimental group at each time of observation). Animals were fasting overnight; the stomach was fully dissected out from its attachment. Each stomach was examined for macroscopical mucosal lesions (Ulcer index) then each stomach was divided into two halves. One half was used for histopathological assessment and PCR. The other half was frozen in liquid nitrogen, freeze-dried (on-70°C) for the biochemical assays.

Induction of gastric ulceration

Rats were fasted for 24 hours, and then refeed with pellet diet. After one hour of refeeding, Indomethacin was administrated subcutaneously at a dose of 20 mg/kg [10,11].

Isolation and culture of adipose derived stem cells

About 900 ml of human lipoaspirate adipose tissue was obtained from elective liposuction procedure for plastic purposes of a female aged 39 years old after a written consent. Adipose tissue was washed extensively with an equivalent volume of PBS with antibiotics about 5-6 times till a clear yellowish adipose tissue was obtained. The lipoaspirate was enzymatically digested with an equal volume of 0.1% collagenase A and kept for 30 minutes in the incubator at 37°C. Enzyme stop medium (DMEM+10% inactivated FBS) was added to stop collagenase activity. The collagenase-digested tissue was centrifuged at 1200 rpm for 10 min to obtain a high-density SVF pellet. SVF pellets were pipetted several times to reduce clumping then passed through a 100 μm mesh to remove cellular debris. Cells were cultured in culture plates and were nurtured with culture medium (DMEM, supplemented with 10% fetal bovine serum and 1% Penicillin-Streptomycin) and incubated at 37°C, humidified atmosphere containing 5% CO_2. When the adherent cells reached 80%-90% confluence, they were harvested. From the harvested cells, CD105+ve and CD45-ve cells were immunomagnetically separated using MACS separation unit and CD105 and CD45 microbeads kits [12,13].

Transplantation of CD105+ve, CD 45-ve cells

After preparation of cells, a dose of 3×10^6 cells/rat was injected i.v. in the tail vein 6 hours after ulcer induction as the ulcers reach maximum size within 6-10 hours [11].

Assessment of gastric mucosal lesions (ulcer index)

The gastric mucosal lesions were expressed in terms of ulcer index (U.I.) according to Peskar et al. which depends on the calculation of a lesion index using a 0-3 scoring system based on the severity of each lesion. Severity factor 0=no lesions; 1=lesions <1 mm length; 2=lesions 2-4 mm length and 3=lesions >4 mm length. The lesions score for each rat was calculated as the number of lesions in the rat multiplied by their respective severity factor. The U.I. For each group was taken as the mean lesion score of all the rats in that group [14].

Histopathological examination

The injury of the stomach was evaluated by histological examination of tissue sections fixed in 10% formaldehyde, embedded in paraffin, and then cut into 3-5 μm sections and stained with hematoxylin-eosin (HE) staining. The histopathological evaluation was performed microscopically by assessing the depth of the mucosal defect which penetrates the muscularis mucosae and muscularis propria including the presence or absence of the inflammatory exudate in the defect (cell debris and neutrophils), fibrinoid necrosis, granulation tissue, fibrous tissue formation and restoration of the glandular architecture in the healing phase.

Measurement of VEGF level in gastric tissue

Glandular mucosa around ulcers (including the ulcer margin and adjacent normal mucosa) were scraped with a glass slide on an ice-cold dish and immediately frozen in liquid nitrogen. The mucosal samples were stored at -70°C until assay then the tissue samples (100 mg) were homogenized for 20 s in ice-cold PBS (10 mM, pH 7.4) and centrifuged at 20,000 g for 20 min at 4°C [15]. VEGF level in the supernatant was measured by an ELISA kit according to manufacturer's instructions.

Measurement of prostaglandin E_2 in gastric tissue

The gastric tissue samples were weighed and prepared by homogenizing it in 1.15% potassium chloride at a ratio of 1:5 (weight/volume) followed by centrifugation at 12000 g for 10 min at 4°C [16]. The supernatant of each sample was used to measure the level of PGE_2 by EIA using a PGE_2-kit according to manufacturer's guide.

Detection of human alu sequences by PCR

PCR for human alu sequences was performed to confirm the presence of transplanted human adipose derived stem cells in recipient rat stomach. First DNA extraction from tissue samples was done using InnuPREP DNA Mini Kit for DNA extraction (Life Science, Germany, Cat. No. 845-ks-10450). Then detection of human alu sequences by PCR was performed on an ABI 7300 Real-Time PCR Detection System using SYBR Premix Ex Taq™ Kit (TaKaRa, Otsu, Japan). The primers used were 5'-CTGGGCGACAGAACGAGATTC- TAT-3' and 5'-CTCACTACTTGGTGACAGGTTCA-3' [17].

Statistical analysis

Statistical analysis was done using SPSS (version 19.0; SPSS INC, Chicago, IL). It includes descriptive statistics and comparative analysis. Paired T-test, ANOVA and post-hoc test were used to compare groups. P-value of <0.001 was considered as statistically significant.

Results

Ulcer index (UI)

The UI of group (T) was significantly lower than Group (D) at days 3, 4 and 5 (P=0.000, 0.000 and 0.000 respectively) which means that adipose derived stem cell treatment has improved the UI. However, UI didn't vary significantly between both groups at day 1 (P=0.102). The highest mean UI was obtained at day 3 for Group (D)=18.7 and the lowest was obtained at day 5 for group (T)=2.8. However, for each group separately, the maximum UI for group (D) was at day 3 and the maximum UI for group (T) was at day 3, which means that in our study, the third day of the gastric ulcer was the day of maximum ulcer index (Figure 1).

Histopathological examination

The gross assessment of gastric mucosal surfaces showed improvement of the stem cell treated Group (T) especially at day 4 and 5 (Figures 2 and 3).

The microscopic assessment of gastric mucosal surfaces revealed that adipose stem cell treatment accelerated the healing of indomethacin-induced gastric ulcer. The improvement of Group (T) was evident at days 3, 4 and 5 (Figures 4 and 5).

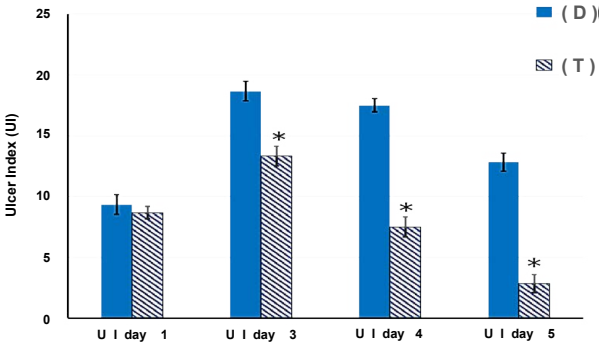

Figure 1: Ulcer index (UI) of groups (D) and (T) along different days of the study. Values represent the arithmetic mean, and error bars represent the standard deviation. Data were analyzed using paired samples t-test. *Significant P value compared to group (D) of the same day, n=6 rats P value ≤ 0.001.

Figure 2: Gross picture of normal rat stomach. Normal gastric mucosal surfaces with no hyperemia, no dot hemorrhages or ulcers

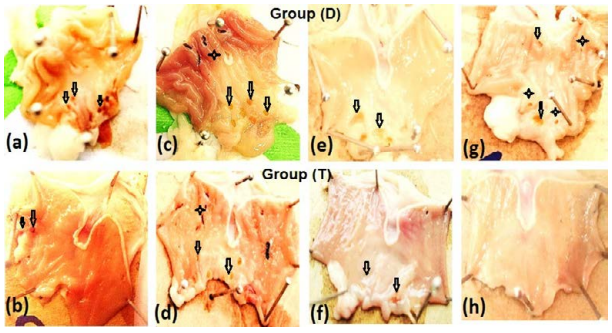

Figure 3: Gross pictures of rat stomachs group (D) and (T) at different days; (a): group (D) day 1 showing mild hyperemia with the presence of multiple small dot hemorrhages mainly in the antral region (arrows). (b): group (T) day 1 showing same gross findings from group D, (c):group (D) day 3 showing marked hyperemia in the body and fundic regions with the presence of hemorrhagic streaks (asterisk) and antral ulcers which are well defined oval or circular and deeper than those in body (arrows). (d): group (T) day 3 showing hemorrhagic streaks, dots (asterisk) and the antral ulcers appear to be shallower and fewer than group D, (e): group (D) day 4 showing absence of body ulcers but antral ulcers are still wide and deep (arrows). (f): group (T) day 4 showing marked improvement due to decreased number of ulcers which are small and shallower than group D (arrows). (g): group (D) day 5 some ulcers are shallow (asterisks) and others are deeper (arrows). (h): group (T) day 5 showing healthy gastric mucosal surfaces that resemble the normal to a great extent with marked improvement than group D.

VEGF level in the gastric tissue

Gastric VEGF results showed that indomethacin decreased the level of gastric VEGF which was significant at day 1, 3, 4 and 5 of the untreated Group (D) comparing with the same days of the normal Group (N). In stem cell treated Group (T), indomethacin decreased the level of VEGF significantly comparing with Group (N) at day 1 only. However, adipose derived stem cell treatment increased the level of VEGF in the stem cell treated Group (T) which was significant at day 1,3,4 and 5 comparing with the same days of Group (D) which means that transplantation of adipose derived stem cells improved the level of VEGF comparing with the untreated group. At days 4 and 5 the adipose stem cell transplantation elevated the levels of VEGF above normal levels to stimulate angiogenesis and healing (Figure 6).

PGE_2 level in the gastric tissue

PGE_2 data analysis showed that indomethacin decreased the level of gastric PGE_2 which was significant at day 1, 3, 4 and 5 of the untreated Group (D) comparing with the same days of the normal Group (N). However in Group (T), indomethacin reduced the levels of gastric PGE_2 comparing with Group (N) at days 1 and 3 only. However, adipose derived stem cell treatment increased the level of PGE_2 in the stem cell treated Group (T) which was significant at day 1, 3, 4 and 5 comparing with the same days of Group (D). It means that transplantation of adipose derived stem cells improved the level of prostaglandin E_2 comparing with the untreated group starting from day1. Also adipose stem cell transplantation returned the levels of PGE_2 to the normal levels at the 4th day (Figure 7).

Detection of human alu sequences in the gastric tissue

The PCR results revealed that at day 1 no amplification occurred in all rats of both untreated group (D) and stem cell treated group (T). At days 3, 4 and 5 amplification occurred in all rats of group (T). In group (D) no amplification occurred at days 3, 4 and 5. This means that the transplanted stem cells homed into the rat stomach starting from day 3 and caused the improvement shown in the histopathology, UI, VEGF and PGE_2 (Figure 8).

Discussion

The present study addresses the role of intravenous transplantation

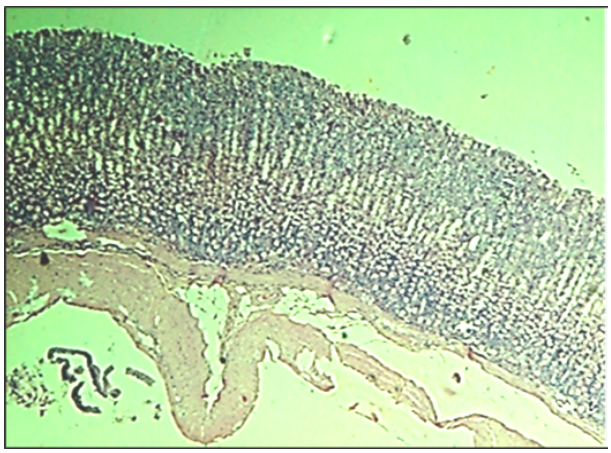

Figure 4: Light micrograph of normal rat stomach (H&E staining) X100 magnification. It shows normal mucosa, submucosa and muscle layer. No ulcers or erosions with normal healthy glandular architecture.

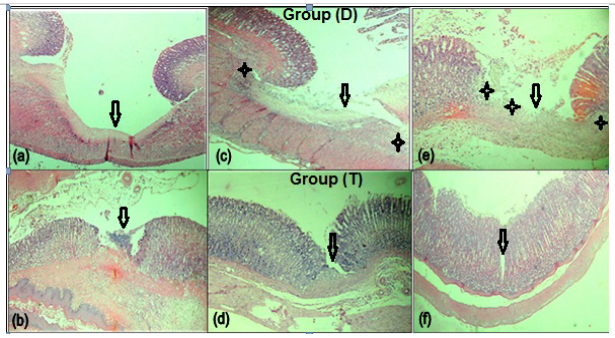

Figure 5: Light micrograph (H&E staining) X100 magnification of rat stomachs group (D) and (T) at different days; (a): group (D) day 3 showing wide ulcer involving the mucosa and submucosa disrupting its normal glandular architecture and exposing the muscularis mucosa (arrow). (b): group (T) day 3 showing an ulcer which is narrower and less deep than group D with mild inflammatory infiltrate and granulation tissue (arrow). (c): group (D) day 4 showing wide deep ulcer reaching superficial muscle layer (arrow) with marked inflammatory infiltrate (asterisks). (d): group (T) day 4 showing an ulcer which is narrower and less deep than group D and limited to the mucosa (arrow). Restoration of the glandular architecture started with less granulation tissue and healthy tissue with minimal inflammatory infiltration, (e): group (D) day 5 showing wide ulcer involving the mucosa and submucosa (arrow) marked inflammatory infiltration (asterisks). There is little granulation tissue indicating the beginning of healing but there is still loss of the glandular architecture, (f): group (T) day 5 showing a slit like ulcer which is very narrow and less deep than group D (arrow) with restoration of the basal layers of the mucosa and restoration of glandular architecture.

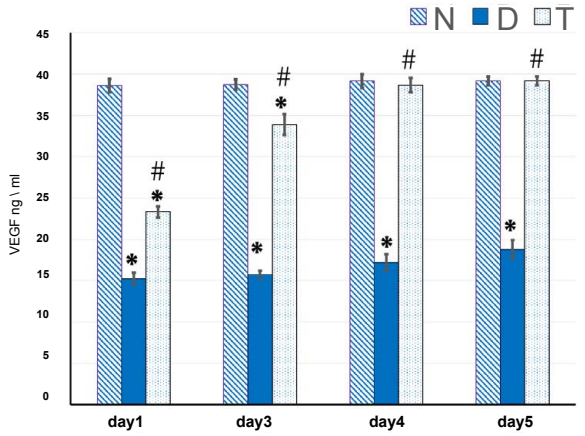

Figure 6: Gastric VEGF levels of groups (N), (D) and (T) at different days. Values represent the mean, and error bars represent the standard deviation. Data are analyzed using One Way ANOVA test and post hoc multiple comparisons test between different groups at each day of the study. * Significant P value compared to group (N) of the same day and #Significant P value compared to group (D) of the same day. P value ≤ 0.001. n=6 rats.

of human adipose-derived stem cells in the healing of indomethacin induced gastric ulceration in rats. The study revealed that stem cells could migrate into then locate in the injured gastric mucosa and significantly accelerate the healing of gastric ulcers which appeared from histopathological examination and assessment of gastric ulcer index. Stem cell injection not only reduced pathological changes in ulcer morphology, but also restored the gastric prostaglandin E_2 level to its normal value. Stem cells also increased the gastric levels of VEGF above normal values which promote the healing process.

The choice of refed gastric ulcer model was in accordance with Satoh et al., researches. They found that in rats fed chow pellets for 1 h after a 24 h fast, indomethacin given within 2 h after refeeding produced chronic antral ulcers mimic human gastric ulcer with regard to location and histology and the lesions reached a maximum size in 6-10 h, penetrated the muscularis mucosae within 3 days, and did not diminish for at least 7 days [11].

In this study we used ADSCs which were CD45-ve and CD105+ve. We didn't use CD34 as marker due to its variable expression in ADSCs unlike other mesenchymal stem cells which are -ve for CD34. Jeffrey et al., reported that the glycoprotein CD34 was present on human ADSCs early in passages [18].

Our results revealed that human alu sequence can be found in the gastric tissue at the 3rd, 4th and 5th after transplantation of 3×10^6 human ADSCs but can't be found after 24 hours of transplantation. Also the alu sequencing can't be found in the non-stem cell treated controls gastric tissue at any day. Chang et al. showed that 48 hours and 72 hours after transplantation of 1×10^7 bone marrow mesenchymal stem cells (BMMSCs) labeled with 5, 6-carboxyfluorescein diacetate succinimidyl ester (CFDA SE), cells were found scattered in the injured gastric mucosa of rats [5]. However, the second day wasn't included in our study. The increased number of stem cells injected in Chang et al. study comparing to our study may be the cause of rapid delivery of the cells to gastric mucosa.

Results of this study were in agree with Chang et al. results regarding ulcer index, histopathology and VEGF levels. However, the study of Chang et al. was limited to the first 72 hours of BMMSCs implantation from rats and in their study they used fasting indomethacin animal

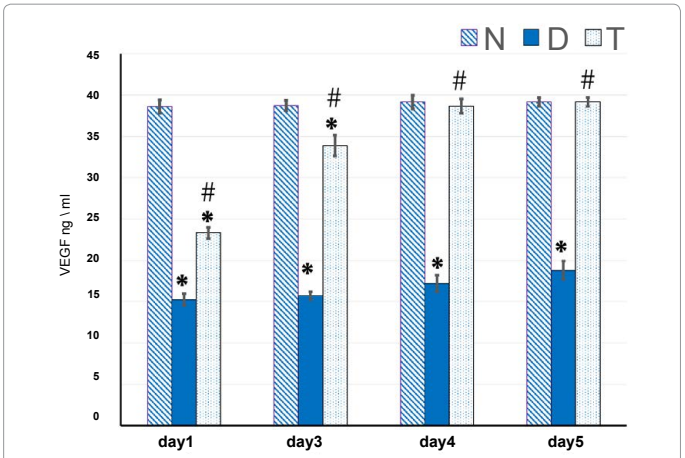

Figure 7: Gastric PGE_2 levels of groups (N), (D) and (T) at different days. Values represent the mean, and error bars represent the standard deviation. Data are analyzed using One Way ANOVA test and post hoc multiple comparisons test between different groups at each day of the study. *Significant P value compared to group (N) of the same day and #Significant P value compared to group (D) of the same day. P value ≤ 0.001, n=6 rats.

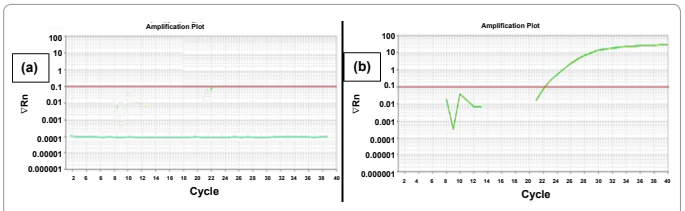

Figure 8: Real time PCR curve for alu gene in rat stomach in stem cell in group (T); (a): group T day 1 PCR curve. The red line is the threshold; the green line shows gene expression. The green line doesn't reach the threshold, no amplification is present (negative sample). (b): group T day 3 PCR curve. The green line shows amplification and cuts the threshold ct=22 (Positive sample).

model through subcutaneous injection of indomethacin (30 mg/kg) into rats after fasting for 24 hours [5]. In both studies the results of ulcer index improved significantly 72 hours after stem cell implantation. In contrast, Yujiro et al. showed that topical transplantation of BMMSCs significantly accelerated the healing of acetic acid-induced gastric ulcers compared with non-transplanted controls (vehicle injection) on day 6 and on day 9, but not on day 3 [19]. The difference between results of our study and Yujiro et al. study may be due to the fact that both models weren't the same or different method of implantation.

We found by ELISA assessment of the gastric tissue level of VEGF that indomethacin significantly decreased the level of VEGF in non-stem cell treated group comparing to normal controls from the first day. However, ADSCs implantation can successfully restore the VEGF surprisingly above the normal level. In contrast with our results, Chang et al. found that the significant improvement in VEGF expressions started at day 3 after BMMSCs transplantation [5]. The increase in the VEGF level in the gastric tissue may be due to either its expression by the ADSCs or its expression from the gastric epithelium under the stimulating effect of ADSCs.

Prostaglandin is one of important defensive factors for protecting gastric mucosa and has important role to maintain homeostasis functions, such as preserving the integrity of mucosa and mucosal blood flow [20].

Our study revealed that PGE_2 level in gastric tissue was markedly decreased after indomethacin injection. However, the stem cell treated group showed restoration of the gastric PGE_2 content by the fourth day. Our experimental results were in line with the previous data showed by Selling et al. which revealed that indomethacin significantly reduced gastric mucosal prostaglandin E_2 (PGE_2) level compared to controls [21]. Treatment with ADSCs significantly increased PGE_2 level when compared to indomethacin treated rats which was explained by Yañez et al. who reported that ADSCs express molecules like prostaglandin E_2 [22].

It is supposed that the acceleration of gastric ulcer healing by ADSCs was due to both VEGF which induce angiogenesis and also due to PGE_2 which induce healing, improve blood supply and stimulate further release of VEGF. Also it is noticed that marked improvements in histopathology, ulcer index, VEGF level and PGE_2 level appeared at the third day which was the day of arrival of stem cells to the gastric mucosa.

In conclusion, intravenous transplantation of human adipose derived stem cells could potentially facilitate the gastric ulcer healing of injured gastric mucosa induced by indomethacin administration. The most probable underlying mechanisms are the migration of stem cells into the injured gastric tissue and the release of growth factors that induce angiogenesis like VEGF and PGE_2. PGE_2 is a very important protective factor of the gastric mucosa against ulceration and induces ulcer healing through improving the blood supply and stimulating the release of VEGF. According to our knowledge, this study was the first to investigate the effect of intravenous implantation of human adipose derived stem cells on the healing of gastric ulcer.

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