

Original Article	EFFICACY OF MESENCHYMAL STEM CELLS IN THE TREATMENT OF GASTRIC ULCERS IN RATS: A HISTOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY <i>Magdy F. Youakim</i> <i>Anatomy and Embryology Department, Faculty of Medicine, Cairo University, Cairo, Egypt</i>
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ABSTRACT

Background: Peptic ulcer is one of the most common gastrointestinal disorders. Although proton pump inhibitors (PPIs) are regarded as the drugs of choice for the treatment of gastric ulcer, they may induce several adverse effects. Therefore, new alternative safer therapy is required. Recent studies have shown that mesenchymal stem cells (MSCs) accelerate the regeneration of ulcerated gastric mucosa.

Aim of work: The aim of this study is to assess the efficacy of MSCs in the treatment of gastric ulcer, and to compare their efficacy to that of the standard PPIs therapy.

Material and methods: The work was performed on 40 adult albino rats, divided into four groups: Group 1 (Control group), Group 2 (Ulcer group), Group 3 (MSCs-treated group) and Group 4 (Omeprazole-treated group). The gastric mucosa was examined for: histopathological changes by light microscope in sections stained with hematoxylin and eosin and for expression of hepatocyte growth factor (HGF) and insulin-like growth factor (IGF) by image analyzer in sections stained immunohistochemically.

Results: MSCs-treated group revealed improvement of histological structure and restoration of the normal architecture of the gastric mucosa. Omeprazole-treated group demonstrated similar results to that of MSCs-treated group. HGF and IGF immunostaining area percent were significantly higher in MSCs-treated group and Omeprazole-treated group when compared to ulcer group.

Conclusion: These results confirm the efficacy of MSCs in the treatment of gastric ulcer which was comparable to that of the PPI omeprazole.

Key Words: Gastric ulcer, MSCs, Omeprazole

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INTRODUCTION

Peptic ulcer is one of the most common gastrointestinal disorders. It affects around 10% of world population (Rao and Venkataramana, 2013). Ulcers occur when harmful factors such as acid, pepsin, helicobacter infection and non-steroidal anti-inflammatory drugs (NSAIDs) overcome the intact mucosal defenses as mucus, bicarbonate and prostaglandins, leading to interruption of the integrity of the mucosa (Laine *et al.*, 2008).

Ulcer healing is a complex process that comprises regeneration of the epithelium, reconstruction of the glands, granulation tissue formation as well as neovascularization. All these events are organized by cytokines and

growth factors. These factors induce cell proliferation and migration during gastric mucosa regeneration; they also help to restore the epithelial and connective tissues as well as the microvessels in the injured mucosa (Jones *et al.*, 1999).

Proton pump inhibitors (PPIs) are powerful blockers of gastric acid secretion. They act by inhibiting the proton pump H⁺ K⁺ ATPase in the parietal cell of the stomach. They are the most effective anti-secretory drugs available and are generally regarded as the drugs of choice for the therapy of acid-peptic disorders as gastric ulcers, duodenal ulcers and gastroesophageal reflux disease (GERD) (Shin and Sachs, 2008; Kedika *et al.*, 2009). However, there is accumulating data linking an association between prolonged

PPIs therapy and bacterial overgrowth within the gastric mucosa. Again PPIs may cause enterochromaffin-like cell carcinoid as result of hypergastrinemia, in addition to several other adverse effects as renal failure and osteoporosis (Jianu *et al.*, 2012; Van Herwaarden *et al.*, 2016). Hence, new alternative safer therapy for the treatment of gastric ulcer is required.

Mesenchymal stem cells (MSCs) are isolated from bone marrow as well as several other tissues. MSCs are characterized by their capability to self-renew and to differentiate into various tissues (Segers and Lee, 2008). Currently, MSCs offer an encouraging alternative for the management of many injured tissues. Several reports have shown that stem cells can play a significant role in curing gut diseases (Andoh *et al.*, 2005; Yan *et al.*, 2009).

AIM OF THE WORK

The aim of this study is to assess the efficacy of MSCs in the treatment of gastric ulcer, and to compare their efficacy to that of the standard PPIs therapy.

MATERIAL AND METHODS

This work was performed at the Faculty of Medicine, Cairo University. The study was carried on 40 adult albino rats weighing 150-200 gm. Rats were housed in wire cages maintained at 25°C, under pathogen free condition and allowed unlimited access to chow and water. All the ethical protocols for animal treatment were approved by the ethical committee of Cairo University.

Preparation of bone marrow (BM)-derived mesenchymal stem cells:

Bone marrow was collected by flushing femurs and tibiae of 6 weeks old male white albino rats with Dulbecco's modified Eagle's medium complemented with 10% fetal bovine serum (GIBCO/BRL). Nucleated cells were isolated by a density gradient [Ficoll/Paque (Pharmacia)] and resuspended in complete culture medium

complemented with 1% penicillin-streptomycin (GIBCO/BRL). Cells were incubated in 5% humidified CO₂ at 37°C for 12-14 days. When large colonies developed, the cultures were washed with phosphate buffer saline twice. The cells were trypsinized with 0.25% trypsin in EDTA (GIBCO/BRL) at 37°C for 5 min. After centrifugation, the cells were resuspended in serum supplemented medium and are incubated in 50 cm² culture flasks (Falcon). Resulting cultures were known to as first-passage cultures. MSCs were identified by their fusiform shape and their capability to adhere to the plastic surfaces as well as by expression of the surface marker CD29 detected by flow cytometry (Abdel Aziz *et al.*, 2007). MSCs were labelled with the PKH26 fluorescent dye according to manufacturer protocol (Sigma Company, Saint Louis, Missouri USA), permitting tracing of the cells in tissues. Cells were centrifuged and washed in serum free medium twice, pelleted and suspended in dye solution. Cells were then injected intravenously into rat tail vein.

Experimental design:

Animals were divided into 4 groups (10 rats each) as follow:

- Group 1 [Control group]: which received no medication.
- Group 2 [Ulcer group]: which received aspirin (from Bayer Pharmaceutical Co.) 100 mg/kg orally via gastric gavage (Seo *et al.*, 2012).
- Group 3 [MSCs-treated group]: which received MSCs single dose of 106 cells, given intravenously through rat tail vein, following ulcer induction (Chang *et al.*, 2012).
- Group 4 [Omeprazole-treated group]: which received omeprazole (from Astra Zeneca Pharmaceutical Co.) 20 mg/kg orally via gastric gavage once daily for one week, following ulcer induction (Swamy *et al.*, 2011).

After seven days rats were sacrificed, their stomach were dissected, cut open, washed with cold saline and the gastric mucosa was examined for:

- Histopathological changes by light microscope in sections stained with hematoxylin and eosin.

- Hepatocyte growth factor (HGF) and insulin-like growth factor (IGF) expression by image analyzer in sections stained immunohistochemically.

Histopathological study:

Sections of 5 µm thickness were cut on a microtome and stained with hematoxylin and eosin (Hx & E) for routine histopathologic examination (Bancroft and Gamble, 2002).

Immunohistochemical study:

Tissue sections were deparafinized, rehydrated and treated with endogenous peroxidase in 0.3% H₂O₂ for 30 min to block endogenous peroxidase activity. The slides were boiled in 10mM citrate buffer, pH 6.0 for 10-20 min then cooled at room temperature for 20 min for antigen retrieval. Positive test slides were incubated with the rabbit polyclonal anti-(HGF) antibody and polyclonal anti-(IGF) antibody with the appropriate dilution range 1:50 for 30 min at room temperature in a humidified chamber. Negative control slides were not exposed to primary antibody. After washing with the phosphate buffer solution, slides were treated with biotin labelled link antibody, then streptavidin conjugated to horseradish peroxidase was used. The diaminobenzidine (DAB) chromogen was applied to visualize antigen antibody reaction (Bancroft and Cook, 1994). All these reagents belong to Universal Labeled Streptavidin-Biotin System, Horseradish Peroxidase (Dako Cytomation, Denmark).

Immuno-histochemical evaluation: Sections were examined by image analyzer computer system using the Leica Qwin 500 software. Five random fields in each specimen were captured using a magnification (X400) to determine the area percentage of immuno-staining. Values were presented as mean and standard deviation and statistically analyzed.

Statistical methods:

Data were analyzed using IBM SPSS advanced statistics version 22 (SPSS Inc., Chicago, IL). They were expressed as mean and standard deviation, then tested for normality using Kolmogorov-Smirnov test and Shapiro-Wilk test. Data were found to be normally distributed so the parametric tests were used for comparison

between groups. Comparison between more than two groups was done using Analysis Of Variance (one-way ANOVA) then post-Hoc "Dunnett t-test" was used for multiple comparison. All tests were two-tailed. A p-value < 0.05 was considered significant.

RESULTS

Histopathologic results:

Group 1:

Examination of histological sections of Group 1 (Control group) showed normal gastric mucosa. The surface was lined by surface mucous cells formed of simple columnar epithelium. The mucosal surface was indented into numerous gastric pits which opened freely onto mucosal surface. The mucosa beneath the pits contains closely packed tubular gastric glands which comprises the bulk of the gastric mucosa. Gastric glands were lined with oxyntic (parietal) cells which predominate the middle region of the gastric mucosa and chief (peptic) cells which predominate the deeper region. The muscularis mucosa appeared thin and adherent to the submucosa (Fig. 1 a-b).

Group 2:

Examination of histological sections of Group 2 (Ulcer group) showed ulcerated mucosal surface with area of superficial epithelial erosion; shedded and exfoliated surface epithelial cells and necrotic debris were seen in the lumen. There was wide lamellar separation between muscularis mucosa and submucosa. Blood vessels were dilated and congested with diffuse inflammatory cellular infiltrate (Fig. 2 a-d).

Group 3:

Examination of histological sections of Group 3 (MSCs-treated group) revealed improvement of histological structure and restoration of the normal architecture of the gastric mucosa. The surface epithelium restored its continuity with mild focal erosions. Gastric tubular glands showed reparative attempts with increased mucosal thickness, less congested blood vessels and fewer inflammatory cellular infiltrate (Fig. 3 a-c).

Group 4:

Examination of histological sections of Group 4 (Omeprazole-treated group) demonstrated similar results to that of Group 3 (MSCs treated

group). Gastric mucosa showed regenerative changes. The surface epithelium showed mild focal erosions. Blood vessels were mildly congested with diminished inflammatory cellular infiltrate (Fig. 4 a-c).

Histomorphometric results:

HGF immunostaining area percent measured using image analyzer was significantly lower in Group 2 (Ulcer group) compared to Group 1 (Control group). Also, it was significantly higher

in Group 3 (MSCs-treated group) and Group 4 (Omeprazole-treated group) compared to Group 2 (Ulcer group) (Tab. 1; Graph 1a; Fig. 5 a-d).

Similarly, IGF immunostaining area percent measured using image analyzer was significantly lower in Group 2 (Ulcer group) compared to Group 1 (Control group). Also, it was significantly higher in Group 3 (MSCs-treated group) and Group 4 (Omeprazole-treated group) compared to Group 2 (Ulcer group) (Tab. 1; Graph 1b; Fig. 6 a-d).

Table 1: HGF and IGF immunostaining area percent in different experimental groups:

	Group 1 Mean ± SD	Group 2 Mean ± SD	Group 3 Mean ± SD	Group 4 Mean ± SD	p-value
HGF	29±2.4	16.1±1.6	23.3±1.4	22.6±2.2	<0.001
IGF	25.7±1.4	10.8±1.0	20.1±2.2	20.6±1.3	<0.001

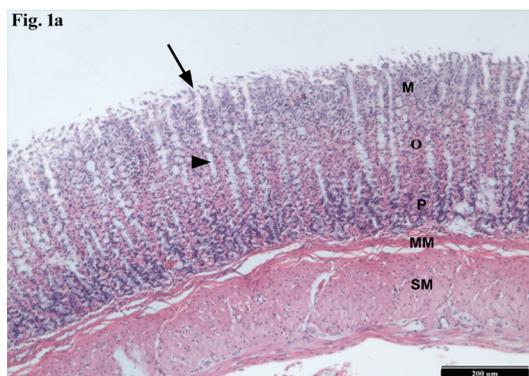


Fig. 1a: (Hx & E x 100).

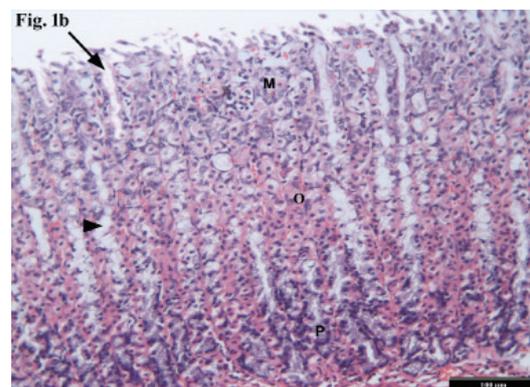


Fig. 1b: (Hx & E x 200).

Fig. 1: Photomicrographs of a section of a rat stomach of Group 1 (Control group) showing normal gastric mucosa, presenting gastric pit (arrow), gastric glands (arrow head). The epithelium consists of mucus-secreting cell layer (M), and acidophilic oxyntic cell layer (O) and basophilic peptic cell layer (P). The muscularis mucosa appears thin (MM) and adherent to the submucosa (SM).

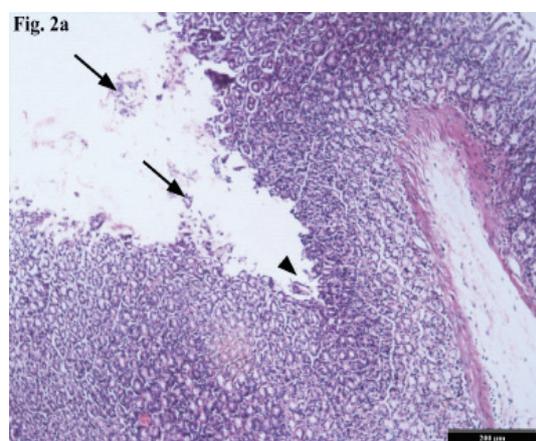


Fig. 2a: (Hx & E x 100).

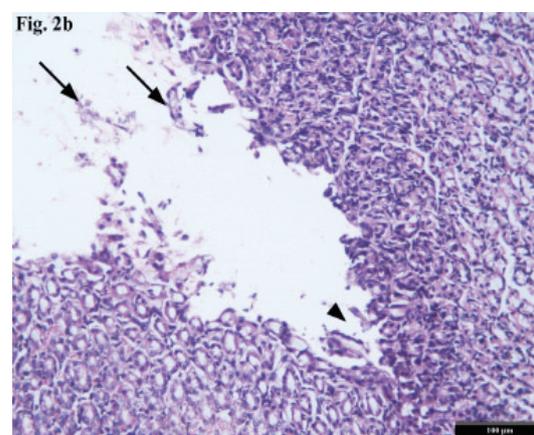


Fig. 2b: (Hx & E x 200).

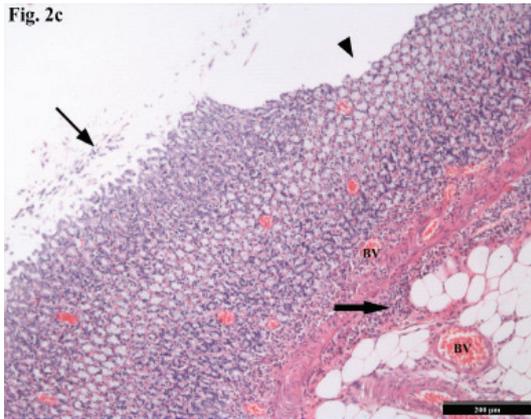


Fig. 2c: (Hx & E x 100).

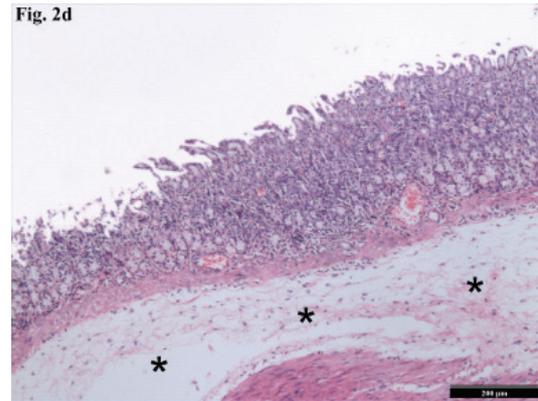


Fig. 2d: (Hx & E x 100).

Fig. 2: Photomicrographs of a section of a rat stomach of Group 2 (Ulcer group) showing shedded surface epithelium (arrow), superficial erosion of gastric mucosa (arrow head), wide lamellar separation between mucosa and submucosa (star). The submucosa shows dilated engorged blood vessels (BV) and diffuse inflammatory cellular infiltrate (thick arrow).

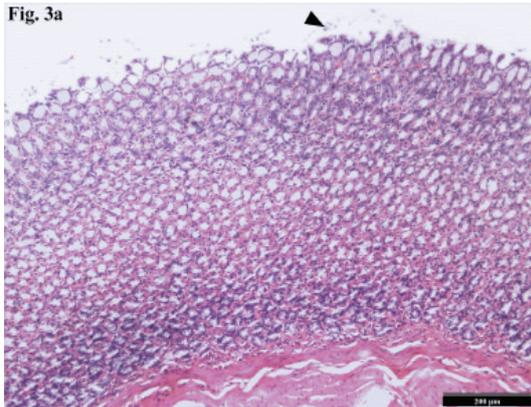


Fig. 3a: (Hx & E x 100).

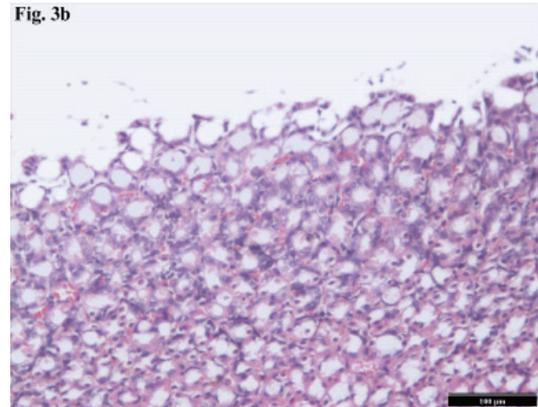


Fig. 3b: (Hx & E x 200).

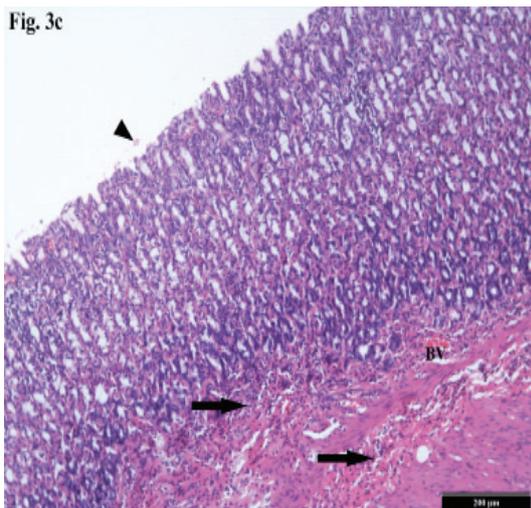


Fig. 3C: Photomicrographs of a section of a rat stomach of Group 3 (MSCs treated group) showing restoration of the normal architecture of the gastric mucosa. The surface epithelium shows minimal shedded epithelium (arrow head) with focal erosions, mildly congested blood vessels (BV) and few inflammatory cellular infiltrate (thick arrow).

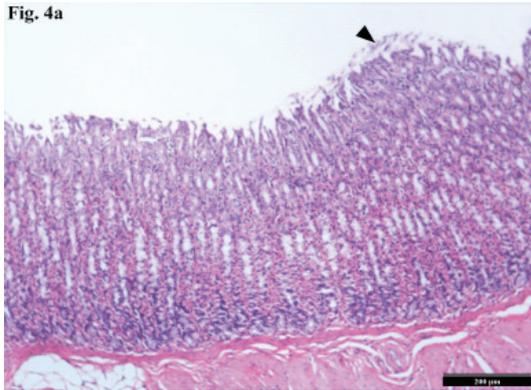


Fig. 4a: (Hx & E x 100).

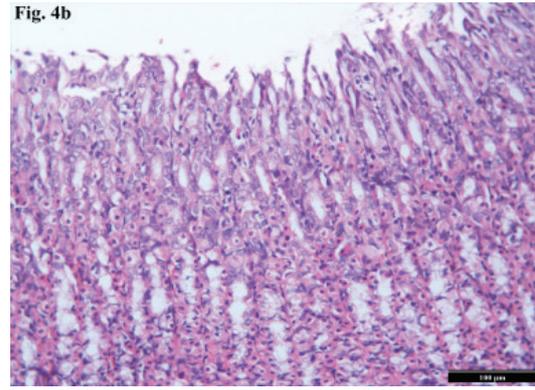


Fig. 4b: (Hx & E x 200).

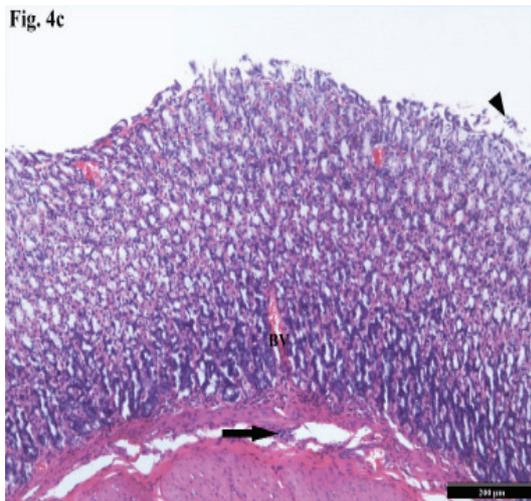
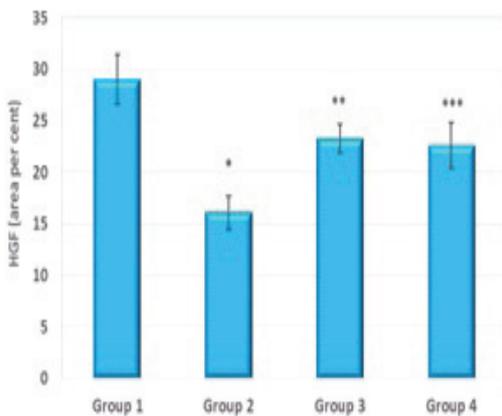
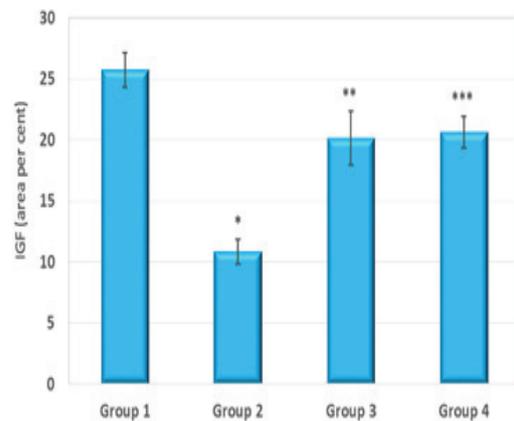


Fig. 4c: (Hx & E x 100).

Fig. 4: Photomicrographs of a section of a rat stomach of Group 4 (Omeprazole-treated group) showing improvement of the histological structure of the gastric mucosa. The surface epithelium shows occasional shed epithelium (arrow head) and focal erosions, slightly congested vessels (BV) and scarce inflammatory cellular infiltrate (thick arrow).



Graph 1a: HGF immunostaining area per cent in different experimental groups.



Graph 1b: IGF immunostaining area per cent in different experimental groups

- * Significant difference in comparison to Group 1 (control group) ($p \leq 0.05$)
- ** Significant difference in comparison to Group 2 (ulcer group) ($p \leq 0.05$)
- *** Significant difference in comparison to Group 3 (ulcer group) ($p \leq 0.05$)

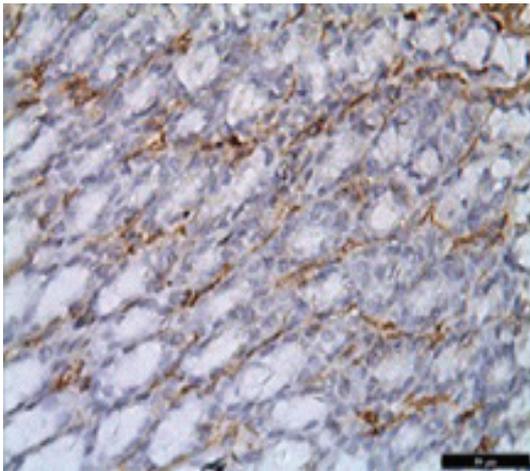


Fig. 5a: Group 1: HGF immunostaining (X400).

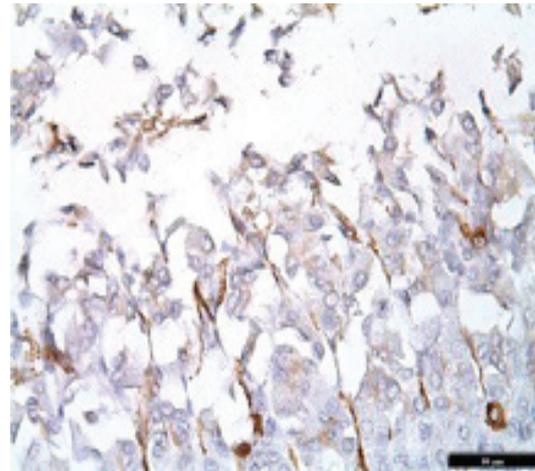


Fig. 5b: Group 2: HGF immunostaining (X400).

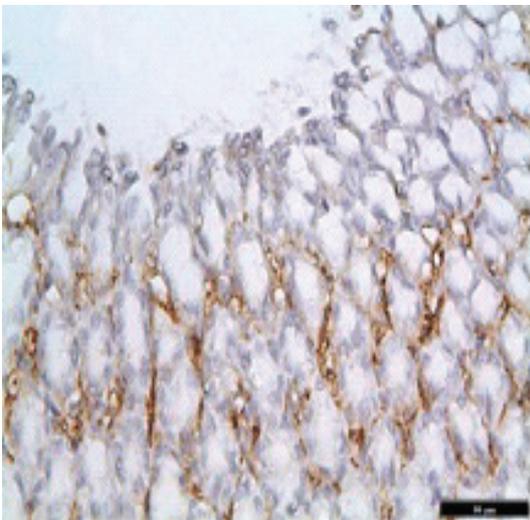


Fig. 5c: Group 3: HGF immunostaining (X400).

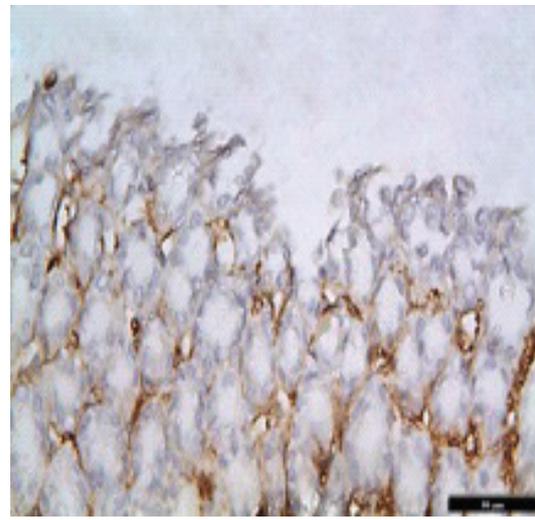


Fig. 5d: Group 4: HGF immunostaining (X400)

Fig. 5: HGF immunostaining in different experimental groups

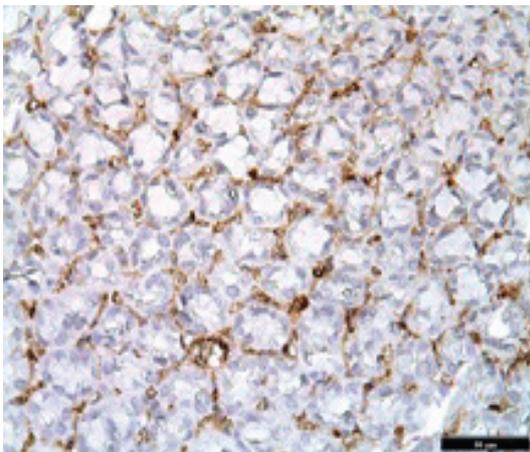


Fig. 6a: Group 1: IGF immunostaining (X400).

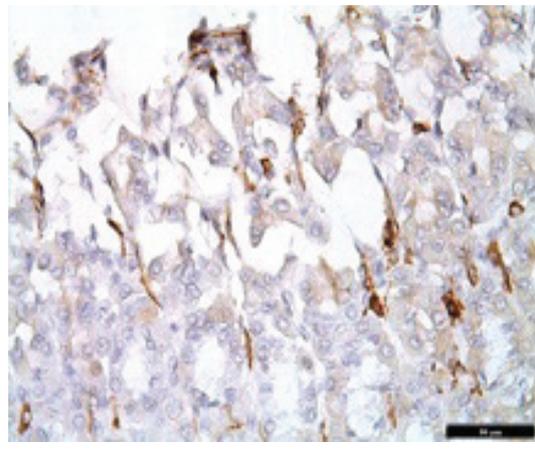


Fig. 6b: Group 2: IGF immunostaining (X400).

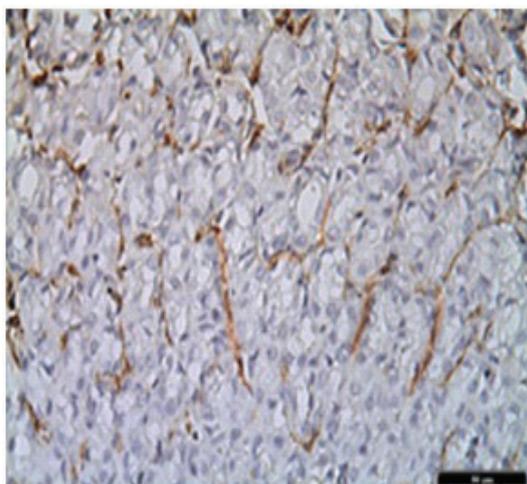


Fig. 6c: Group 3: IGF immunostaining (X400)

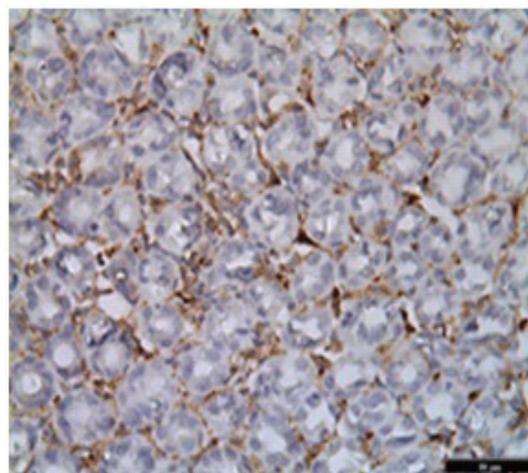


Fig. 6D: Group 4: IGF immunostaining (X400).

Fig. 6: IGF immunostaining in different experimental groups.

DISCUSSION

MSCs are multipotent cells, characterized by being able to migrate through tissues and to differentiate into several of cell types according to the surrounding microenvironment (Phinney and Prockop, 2007). MSCs have great therapeutic potential in many human diseases. The interest in MSCs-based therapies for gut injuries is growing nowadays. Reports have shown that bone marrow-derived stem cells contribute to regeneration of ulcerated gastric mucosa (Okumura *et al.*, 2009).

MSCs accelerate the healing of gastric ulcers by decreasing inflammation phase and stimulating of proliferative-reparation phase of the regeneration process (Askarov, 2008). MSCs have shown great capacity to differentiate into epithelial cells of the gut (Krause *et al.*, 2001), and therefore, aiding to regenerate damaged epithelium in the gastrointestinal tract (Okamoto *et al.*, 2002). MSCs promote also the regeneration of the connective tissue components (Tarnawski, 2005). Again, they stimulate neovascularization, improving gastric mucosa microcirculation, and accelerating ulcer healing (Askarov and Onischenko, 2008).

This study examined the therapeutic potential of bone marrow-derived mesenchymal stem cells in the treatment of experimental gastric ulcers in rats. In the present work, MSCs stimulate ulcer healing as observed in sections in the form of improvement of histological structure

and restoration of the normal architecture of the gastric mucosa. Together with reduced blood vessels congestion and inflammatory cellular infiltrate. Similar findings were observed by several authors who noticed that MSCs accelerate gastric ulcers healing and assumed that MSCs transplantation can be used as an alternate method for ulcer treatment (Chang *et al.*, 2012; Askarov, 2008; Askarov and Onischenko, 2008).

However, our study did not only show the beneficial effect of stem cells on ulcer healing but also offered more profound explanation of the mechanism of these stem cells. This work demonstrated that the role of stem cells is not restricted on migration to the site of gastric injury, where they consequently differentiate into gastric cells replacing the damaged one as described by some authors (Komori *et al.*, 2005), but also was accompanied with a significant increase of growth factors. In the current work, HGF and IGF were significantly higher in Group 3 when compared to Group 2 proving that treatment with MSCs is accompanied by an increase in growth factors which in turn accelerate the healing of gastric ulcer.

Growth factors are suggested by many authors to be involved in gastric mucosal repair. They are important for proliferation and migration of epithelial cell, regeneration of gastric glands as well as neovascularization (Tarnawski and Ahluwalia, 2012). Some authors have found that of growth factors administration stimulate ulcer repair while the inhibition of their effects by

antibodies results in ulcer delayed healing (Milani and Calabrò, 2001).

HGF acts principally upon epithelial cells. It has a major role in epithelial regeneration and wound healing. Some authors also considered HGF to be the most powerful mitogen for gastric epithelial cells, as for hepatocytes. HGF was found to be expressed by fibroblasts at the gastric ulcers edges, confirming its importance in ulcer repair, where it accelerates the proliferation and migration of the gastric epithelial cells (Takahashi *et al.*, 1995; Takahashi *et al.*, 1996; Kinoshita *et al.*, 1997). Similarly IGF was found to stimulate the proliferation, differentiation and survival of the epithelial and mesenchymal cells, thus helping to accelerate gastric ulcer healing (LeRoith *et al.*, 1995; Coerper *et al.*, 2001; Zhao *et al.*, 2009).

Hence by their ability to differentiate into gastric cells replacing injured ones and their ability to increase growth factors, stem cells have shown evident efficacy in treating gastric ulcers.

In the current work, the effect of PPI omeprazole on gastric ulcer healing was also studied. Omeprazole treatment improved gastric ulcer as was observed in histological sections. The beneficial effects of MSCs observed in this study were comparable to that of PPIs which are actually considered the most effective treatment of gastric ulcers.

CONCLUSION

The results obtained in the present work confirm the effectiveness of MSCs in the treatment of gastric ulcer, which was comparable to that of the PPI omeprazole. Thus, suggesting that MSCs could be adjuvant or even safer alternative therapy than PPIs, with the benefit of avoiding the side effects resulting from the use of these drugs.

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فاعلية الخلايا الجزعية في علاج قرحة المعدة في الفئران: دراسة هستولوجية و مناعية هستوكيميائية

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ملخص البحث

المقدمة: تعتبر قرحة المعدة من أكثر أمراض الجهاز الهضمي شيوعاً. بالرغم من أن موانع مضخات البروتون يعتبروا العقارات المفضلة لعلاج القرحة إلا أنهم قد يتسببوا في العديد من الأعراض الجانبية. من هنا الحاجة لعلاج بديل أكثر أماناً. الدراسات الحديثة أظهرت إن الخلايا الجزعية تسرع من تجديد الغشاء المبطن المتقرح للمعدة.

الهدف من البحث: تقييم فاعلية الخلايا الجزعية في علاج قرحة المعدة و مقارنتها بفاعلية موانع مضخات البروتون .

الطرق والمواد المستخدمة: أجريت هذه الدراسة على ٤٠ فأر بالغ مقسمين على ٤ مجموعات: المجموعة الأولى (مجموعة ضابطة)، المجموعة الثانية (مصابة بالقرحة)، المجموعة الثالثة (تلقت علاج بالخلايا الجزعية)، مجموعة رابعة (تلقت علاج بالأوميبرازول). وقد تمت دراسة النسيج المبطن للمعدة باستخدام المجهر الضوئي لدراسة عينات تم صبغها بالهيماتوكليسين والايوسين وكذلك دراسة عامل النمو الكبدى و عامل النمو المشابه للإنسولين باستخدام جهاز المحلل الضوئي لعينات تم صبغها بالصبغة المناعية الهستوكيميائية.

النتائج: أظهرت المجموعة المعالجة بالخلايا الجزعية تحسن في التركيب النسيجي للغشاء المبطن للمعدة. كذلك أظهرت المجموعة المعالجة بالأوميبرازول تحسن مماثل. كما كان عامل النمو الكبدى و عامل النمو شبيه الإنسولين أعلى في المجموعة المعالجة بالخلايا الجزعية و المجموعة المعالجة بالأوميبرازول مقارنة بالمجموعة المصابة بالقرحة .

الخلاصة: أثبتت الدراسة فاعلية الخلايا الجزعية في علاج قرحة المعدة و كانت تلك الفاعلية مماثلة لفاعلية الأوميبرازول.

مفاتيح الكلمات: قرحة المعدة - الخلايا الجزعية - الأوميبرازول.