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Effect of different energy densities of shock wave therapy on wound healing: experimental study

Hesham Galal Mahran El-Sayed*[1], Mohamed Mohamed Ibrahim Ali[1], Ali Abd El-Monsif Thabet,[1] Abdelgalil Allam Abdelgalil[1],and Wael Amin Nasr El-Din[2,3]

[1]Physiotherapy and Rehabilitation Department, Faculty of Applied Medical Sciences, Umm Al-Qura University, Mecca, **Saudi Arabia**

[2]Department of Human Anatomy and Embryology, Faculty of Medicine, Suez Canal University, Ismailia, **Egypt**.

[3]Department of Anatomy, Ibn Sina National College for Medical Studies, Jeddah, **Saudi Arabia.**

***Correspondence:** heshammahran75@yahoo.com **Received 01-01-2020, Revised: 18-01-2020, Accepted: 19-01-2020 e-Published: 30-01-2020**

Objective: To evaluate the efficacy of various energy densities of shock wave therapy on wounded rats and to compare their effects. Design: Randomized, controlled trial. Animals: sixty rats; adult, male, and albino type. Interventions: A wound area of six-centimeter square was performed post-anesthesia after that rats were divided into group (A) (Twenty rats, six hundred shocks per session for six sessions, energy density per shock 0.1 millijoules/mm^2), group (B) (Twenty rats, six hundred shocks per session for six sessions, 0.05 milli joules/mm^2) and group (C) (Twenty rats, as control group or shockwave in shutdown mode group). Measures: At the end of the 1st and 2nd weeks, wound surface areas and contraction rate were measured by planimeter. Results: By the end of 1st and 2nd weeks, group (A) and (B) showed more significant shrinking in wounded area (WSA) in addition more significant increase in contraction rate, when compared respectively to those measures in group (C) in addition more better results in group (A) was found in comparison to group B Conclusion: Shock Wave Therapy has facilitating effect on wound healing at both energy density levels; 0.1 milli Joules /mm2 and 0.05 milli Joules/mm2, in addition, more positive healing results were gained at 0.1 milli Joules /mm^2 energy density.

Keywords: Wound, Rats, shock wave.

INTRODUCTION

Wound healing is a well-planned, interlaced series of biological occasions on different scales; systemic, cellular, and molecular. It includes a wide diversity of cells and changes, which are linked to the overlapping period and the existence of cell-to-cell signaling molecules inside the injured tissue. The most crucial evidence of the regeneration of damaged tissue during wound healing is the functional vasculature restoration (Milch et al., 2010), which happens to a great extent through angiogenesis, (Machado et al., 2011; Tonnesen et al., 2000), vasculogenesis, and new small blood vessels formation (Suh, 2000; Velazquez, 2007). The failure of advance in the healing procedure exposes the wound to contamination and damage of the underlying tissue, which ordinarily prompts more morbidities (Galiano et al., 2004).

The essential targets of wound treatment are tight wound closure and complete cure. The ideal management of acute wounds involves the arrangement of wound bed, surgical and enzymatic cleaning of the wound followed by utilization of sterile dressings to supply a wet medium or primary surgical closure or with flaps or grafts of skin. These treatments are a time-consuming and costly burden. Consequently, the requirement for a novel, safe, effective and financially-effective therapy is demanding and many types of research had been dedicated to the development of wound treatment. Furthermore, adjunctive therapy with ultrasound, negative pressure wound therapy (NPWT) and hyperbaric oxygen therapy (HBOT) are reported for the cure of acute and chronic wounds (Freedman and Stern, 2004; Antonic et al., 2011).

Extracorporeal shock wave (ESW) is a longitudinal acoustic wave induced by electrohydraulic, electromagnetic, or piezoelectric techniques that diffuse in tissue with a sudden rise from ambient pressure to supreme pressure at the wavefront. Primarily, high energy ESW was utilized in the fragmentation of the urinary stones. After that, shockwave treatment turned into an ideal therapy for different widespread orthopedic diseases like tennis elbow and plantar fasciitis (Wang et al., 2001). Shockwave therapy is used successfully for the treatment of aseptic bone necrosis and ununited fractures in long bones **(**Schaden et al., 2001**).** On the contrary to the mechanism of shockwave therapy in the treatment of stones of kidney therapy, the main orthopedic objective of treatment by shockwave is to enhance the renewal of tissue but not break the tissue **(**Wang et al., 2002 a,b**).** Recently, various chronic wounds, including diabetic and vascular ulcers, burn wounds, and bedsores had been showed magic amelioration under low-energy ESW therapy (Meirer et al., 2005; Saggini et al., 2008; Schaden et al., 2007; Wolff et al., 2011).

Although the mechanism of action of the ESWT is still under research, the main catalyst in wound healing may be explained by cavitation phenomenon of the shock wave; in which the shock wave is transformed into complex biological responses included in the improvement of tissues perfusion and angiogenesis promoting wound healing amelioration (Mittermayr et al., 2012). The scope of parameters utilized for wound healing is energy flux density from 0.05 milli joules/mm^2 to 0.20 milli joules/mm^2, frequency of pulse from 3 to 5Hz (Antonic et al., 2011). ESWT is categorized according to its levels of energy. Shockwaves with low-energy has an energy flux density with an upper limit of 0.08 milli joules/mm^2, while, device with moderate level of energy provides intensity ranged above the upper limit of low level and up to 0.28 milli joules/mm^2 and finally shock waves device with high energy produces energy flux density up to 0.6 milli joules /mm^2 (Minilith, 1997; Rompe, 1996).

There were no fixed therapeutic strategy for the treatment by shock wave used in wound healing as there were various doses of shock wave therapy used in many studies and had considerable positive impact on healing as follow; Saggini et al treated various species of ulcers (venous ulcer, posttraumatic ulcer, diabetic ulcer) by utilizing low-intensity shockwave treatment with following characters; amount of pulses: 100 pulses/cm^2, energy flux density: 0.037 mJ/mm^2, frequency: 4 pulses/sec and studies founded that a marvelous amelioration in ulcer healing in group exposed to shockwave when compared to group received wound care **(**Saggini et al.,2008**).** Moretti et al., used shock wave with energy flux density was 0.03 millijoules/mm^2 which considered as low-intensity shock wave, and amount of pulses were 100 pulses per cm^2 as a therapy for patients presented with diabetic plantar ulcers and there were remarkable rapid healing and higher rate of epithelial regeneration as compared to control group ($p < 0.001$) (Moretti et al., 2009).

Ottoman et al., induced split-thickness skin graft operation then utilized medium intensity shockwave for healing donor sites. They used shockwave therapy with features; energy flux density: 0.1 mJ/mm^2, amount of pulses: 100 pulses/cm^2 and a fascinating result showed faster epithelial restoration in the ESWT when compared control group ($p < 0.0001$) (Ottomann et al.,2010). In a pilot study with no control group, Arnó et al., induced deep partial and full-thickness burn wound and applied extracorporeal shockwave therapy with the following characters; 0.15 mJ/mm^2 as energy flux density and 500 pulses. The results demonstrated the enhancement of wound perfusion. So our purpose in the study was directed to investigate the shock wave different doses effect on the healing of wounded rats through applying various energy densities (Arno et al., 2010).

MATERIALS AND METHODS

Experimental animals:

A total of sixty adult male albino rats (4 months old and weighed 200-250 gm) were brought from the house of animal in Medicine Faculty, University of Umm Al Qura, Mecca, KSA. The rats were separately put in stainless steel cages in adjusted circumstances at a 12:12-h dark-light cycle with a temperature; 23-25°C and 50% humidity. a pellet diet and tap water were introduced throughout the whole period of the experiment,.

Excisional wound:
By using electrical dipper the upper dorsal skin of all sixty rats was shaved and sterilized with 70% alcohol. Furthermore, rats were exposed to anesthesia by diethyl ether inhalation. The upper dorsal aspect of all animals is then exposed to a full-thickness excisional wound by excision of a wound area of size about 2x3 cm. All surgical operations were performed by only one investigator.

Design of Experiment:
The type of study is a randomized controlled trial. Animals were randomly assigned into three equal groups after exposure to full-thickness wound; **A, B** and **C**. (20 animals per each group). Two hours after the surgical intervention, the therapy was commenced all studied groups.

Procedures
A)-Treatment:
- Wounds of all animals were sterilized by alcohol then the cavity of the wound was plugged by sterile sonic gel. To prohibit any contamination to the utilized device, all wounds and surrounding tissues were covered by a sterile plastic drape. Over the plastic drape, we placed the extracorporeal shock wave applicator (1**5 mm^2**) then started the movement of this device over the cavity of the wound and its margins. In group **(A)**; The rats exposed to six sessions of treatment with following shockwave intensity; every session composed of 600 shocks, four shocks per second, intensity per shock was 0.1 milli joules/mm^2 and time per session was two and half minutes. In group **(B)**: The rats were exposed to six sessions of treatment with following shockwave intensity; every session composed of 600 shocks, four shocks per second, intensity per shock was 0.05 millijoules /mm^2 and time per session was two and half minutes. In the control group **(C)** The rats exposed to shockwave in shutdown mode for two and a half minutes. to control the effect of shock wave applicator on the wound and sonic gel effect. Two sessions every week were performed in all groups. Following every session, we removed gel and plastic drape then dried the wound.

B- Assessments

1- Measurement of the wounded surface area:
Based on the method of the planimeter, the wounded surface area (W.S.A) was calculated through applying a piece of disinfected transparency film on each wounded area then on the film the wound perimeter was defined or traced with a marker of fine-tipped. For each wound, we utilized individual transparency. Then, we applied the traced transparency film on calibrated graph paper, and the numbers of the square millimeters over the calibrated graph paper were counted (we counted only full1millimetre squares in the perimeter) then the area was transformed into square centimeters. To ensure accurate measurement, we repeated the tracing process three times. WSA was defined as the calculated mean of the 3 measurements (Zaffuto et al., 1990). These measurements were calculated on the day (0), at the end of week 1 and at the end of week 2**.**

2- Wound contraction rate:
We measured the traced area and calculated the healed area expressed as (1-A1)/A0 x100 from the original area of the wound (A0) and the unhealed area (A1).

Statistical procedure:
- SPSS program v(16) was applied to collect and analyze our results. Means and standard deviations were estimated. Mean values within a group were compared using repeated-measures ANOVA, while one way ANOVA was used in order to compare mean values between groups. When the probability value was less than (0.05), a significant result should be considered.

RESULTS
In our study, we obtained sixty adult male albino rats with uniform features; weighed about 200-250 gm, aged approximately 4 months, the same kind of food was provided to all rats and exposed to the same surgical operation with only one investigator.

Wounded surface area (WSA) and contraction rate results
The data included within table (1) and figure (1) showed that; consecutive decrease in the surface area of the wound during the stages of therapy (Day (0), week 1 and week 2) in all three groups and reached highly significant level as *p*-value < (0.05) as results were analyzed by repeated-measures ANOVA.

At 1st week, wounded area mean values in three groups were around 6cm^2 and analysis of data by ANOVA showed no significant difference among the studied groups as *p*-value (0. 0.57) as well as more analysis by Post Hoc test confirmed that no significant difference among the studied groups as follows; the wounded area mean value in group (A) in comparison to mean value in group (B), the p-value was (0.6). The wounded area mean value in the group (A) in comparison to mean value in the group (C), the p-value was (0.59). The wounded area mean value in the group (B) in comparison to mean value in the group (C), the p-value was (0.3)(Table 1) and (Figure 1).

Table 1: Comparison of Means of wound surface areas (WSA) at (Day (0), 1st and 2nd weeks) within the group and between groups.

	Group A	Group B	Group C	P value	Post Hoc test (P values)
Day(0)	6.08±0.13	6.11±0.11	6.05±0.12	0.57	$(0.6)^{ab}$ $(0.59)^{ac}$ $(0.3)^{BC}$
1st week	1.87±0.3	2.21±0.38	2.69±0.21	0.0001	$(0.019)^{ab}$ $(0.0001)^{ac}$ $(0.020)^{BC}$
2nd week	0.02±0.01	0.16±0.08	0.5±0.24	0.0001	$(0.048)^{ab}$ $(0.0001)^{ac}$ $(0.0001)^{bc}$
P value	0.00001	0.00001	0.00001		
LSD test	$(0.00001)^{0,1st}$ $(0.00001)^{0,2nd}$ $(0.00001)^{,1st,2nd}$ for three groups				

(*Probability value*) ^{ab}: Group A in comparison to Group B, (*Probability value*)^{ac}: Group A in comparison to Group C, (*Probability value.*)^{bc}: Group B in comparison to Group C.

(*Probability value.*)^{0,1st}: day 0 in comparison to 1st week, (*probability value*) $^{1st, 2nd}$:1st week in comparison to 2nd week, (*probability value*) $^{0, 2nd}$:0 day in comparison to 2nd week.

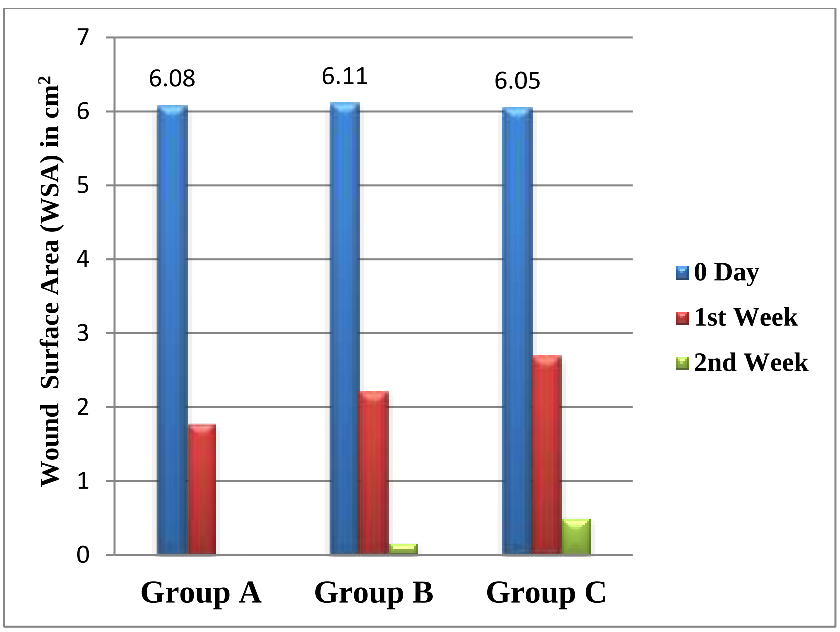

Figure 1 : Wound area means values comparison within each group.

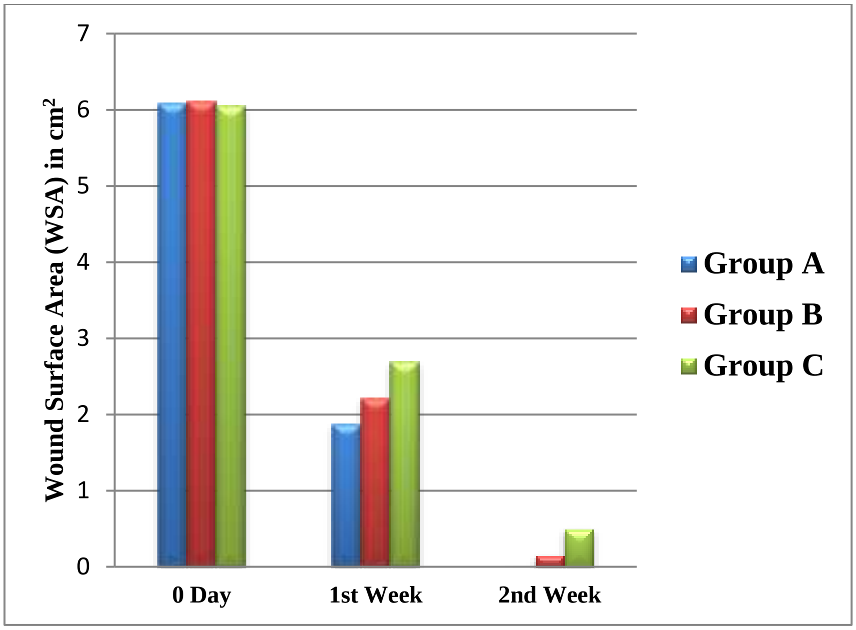

Figure 2: Wound area means values comparison between groups at each assessment phase.

By the end of week 1, the wounded area mean value in group (A) was (1.87±0.3) cm^2 and shrinking rate of % (69.2±5.22) while the mean of WSA in group (B) was (2.21±0.38) cm^2 with shrinking rate of % (63.8±6.2) while it was (2.69±0.21) cm^2 in group (C) and its shrinking rate of % (55.5±3.8). Data analysis by ANOVA showed a difference among the studied groups which reached a highly significant level as the *p*-value (0.0001) and using of Post Hoc test confirmed the last results as showing that significantly, there were high differences between wounded area mean values in groups; group (A) and group (B), group (A) and group (C), group (B) and group (C) as *p*-value (0.019), (0.0001), (0.020) respectively.

At the week 2, the wounded area mean value in group (A) was (0.02±0.01) cm^2 with shrinking rate of % (99.6±0.23), the wounded area mean value in group (B) was (0.16±0.08) cm^2 and shrinking rate of % (97.3±1.3), while it was (0.5±0.24) cm^2 in group (C) with shrinking rate of % (91.7±4). These results showed a highly significant difference among the studied groups as *the p*-value (0.0001) when the data analyzed by one way ANOVA. Data confirmation by Post Hoc test showed; highly significant differences between wounded area mean values in groups; group (A) versus group (B), group (A) versus group (C) and group (B) versus group (C) as *p* values are (0.048), (0.0001) and (0.0001) respectively.

DISCUSSION

A rat model of excision wound was induced in this study for investigating the effect of various energy densities of shockwave therapy on wound healing and detecting the best energy density for treatment. Our results presented a proof that at first, therapy with shock wave possess a facilitating influence on wound healing, secondly, wound healing process may be affected according to adjustment of energy densities of treatment with shock wave, lastly, the study decided which energy density has the best healing effect; as our study results demonstrated that; comparing the studied groups at the end of week 1 and week 2, showed that the process of healing in groups A and B which evaluated by wound surface shrinking and increased the rate of healing rate is better than that in group C, these results are elucidated due to healing effect of shockwave therapy.

Our findings are in match with novel previous studies which induced wound in animal models and approved that ESWT may be beneficial and efficient in healing through its stimulation of many endogenous growth factors (Davis et al.,2009; Zins et al.,2010; Bosch et al.,2009, Martini et al.,2003). It promoted the induction of endothelial progenitor cells, (Aicher et al.,2006) and recruitment of angiogenesis (Zimpfer et al.,2009; Sobczak and Kasprzak, 2010). Nitric oxide (NO), a powerful vasodilatation mediator, was highly elevated following the ESWT therapy leading to enhancement of tissue perfusion. Shockwave promotes NO synthesis by means of increased NO synthase expression. The powerful endogenous pro-angiogenic and vasculogenic factor, Vascular endothelial growth factor (VEGF) is acutely motivated after the shockwave, (Yip et al.,2008) and VEGF receptors are more greatly expressed in the aimed tissue (Ma et al.,2007).

ESWT applied to animal models has been demonstrated to create an appropriate molecular medium in the wound tissue, quell chemokines and early pro-inflammatory cytokines, and promote expression of numerous wound healing linked genes (Stojadinovic et al., 2008; Zins et al., 2010)

Studies have shown that shockwaves expressed an anti-inflammatory mechanism through attenuated early local inflammatory responses (low levels of macrophage-derived inflammatory protein (MIP-1a, MIP-1b) in grafts in ESWT treated animals (Zins et al., 2010; Kuo et al., 2009).

ESWT promotes the proliferation of cells, motivates extracellular matrix metabolism, reduces apoptosis in the wound tissue (Aicher et al., 2006; Chao et al., 2008)

Furthermore, analysis of our results at the end of 1st and 2nd weeks reported that better wound healing was elicited in group A than in group B in the form of a significant decrease in the mean of wounded areas and a significant increase in the mean of contraction rate in group (A) when compared to those of group (B). These results may be due to the effect of the double dose of the shockwave (0.1mmJ/cm2) in the group (A) as compared to the dose received in the group (B) (0.05mmJ/cm^2).

Our data and illustrations, demonstrated that the therapy of a dose at 0.1mmJ/cm2 of the shock wave is more enhancer of healing than 0.05 milliJoules/cm^2 in and this confirmed that the energy flux density in a dose of 0.1 mJ/mm2 is the most efficient intensity for treatment.

Our results are in match with a previous study which induced deep partial-thickness burns then examined the skin regeneration under the influence of ESWT. Rats of a group (1) received 500 shocks of ESWT with an energy flux density of 0.11 mJ/mm2 and a frequency of 240/min but not to group (2). ESWT improved the ratio of wound closure in the group (1) more than group (2) as (P < 0.05). The rate of epithelial regeneration was significantly ameliorated on day 15 (P < 0.05). In the ESWT group, the wound score was significantly increased. ESWT promotes regeneration of skin after deep partial-thickness burns in rats (Wang et al., 2009).

A motivating clinical study was conducted by Wang et al. comparing ESWT and HBOT in diabetic foot ulcer treatment. In the ESWT group, four hundred pulses per cm^2 at an energy flux density of 0.11 mJ/mm2 was applied to the ulcer every 2 weeks. The HBOT was implemented applying sealed multiple chambers at a pressure of 2.5 atmospheres absolute for 90 minutes total. Complete ulcer healing appeared in 31% of the ESWT group versus 22% in the HBOT group with a statistically significant difference. Moreover, more than 50% amelioration in the wound surface appeared in 89% of shock wave-treated ulcers compared with 72% of HBOT-treated ulcers (Gabriel et al., 2014).

In a randomized study conducted on 44 patients presented with acute second-degree burns; they were randomly divided to receive the traditional treatment (debridement of burn wound with local antiseptic treatment) with (n = 22) or without (n = 22) defocused ESWT (100 impulses/cm2 at 0.1 mJ/mm2) placed once to the burn following debridement. The usage of one dose of defocused shock wave treatment to the burn after the traditional therapy greatly promoted and ameliorated the rate of epithelial regeneration (Christian et al., 2011).

In a study, investigated a rat model with diabetic wound, the efficacy of low-energy ESWT on collagen content in wound tissues and its effectiveness in incisional wound healing were examined. Rats received ESWT at various times after wound induction. 100 impulses focused ESW (flux density level: 0.11 mJ/mm2; 3 Hz) per centimeter wound length were placed on the wound in ESWT-1 and ESWT-2 groups. Wounds were smeared with the transmission gel in non-diabetic and diabetic groups, but no shock wave impulse was applied. On days 7 and 14 following wound induction, all rats were sacrificed. After ESWT administration, the fibroblasts number was greatly increased, and new copious collagen fibers were located at the wound. Moreover, On day 7 post-wounding after ESWT TGF-β1 expression was up-regulated. These data indicate that applying energy ESWT with an intensity of 0.11 mJ/mm2 in diabetic rats can promote the contents of collagen, accelerate the force of wound breaking and ameliorate healing of the incisional wound. TGF-β1 expression up-regulation leads to increased collagen content at the site of wound tissues (Guang et al., 2011).

CONCLUSION

Shock Wave Therapy has facilitating effect on wound healing at both energy density levels; 0.1

milli Joules /mm2 and 0.05 milli Joules/mm2, in addition, more positive healing results were gained at 0.1 milli Joules /mm2 energy density.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

HGM designed and performed the experiments and also wrote the manuscript, MMIA and AAT performed animal treatments AAA and WAN performed data analysis, designed experiments and reviewed the manuscript. All authors read and approved the final version.

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