Efficacy of Negative Pressure Therapy (NPWT) in the Management of Wounds of Different Etiologies

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The objective was to assess the role of negative pressure wound therapy (NPWT) in the management of wounds of various etiologies, infected or not, acute or chronic. The study was conducted in a group of 37 patients (24 men and 13 women) aged 26 to 86 years with acute or chronic wounds, posttraumatic or due to chronic diseases located on the lower limbs or following oncological abdominal surgery. In all cases a Vacuum Assisted Closure (VAC) system was continuously applied using a subatmospheric pressure ranging from 90 to 120 mmHg. Beside sex, age and etiology of soft tissue defect the following parameters were studied: surgical treatment performed prior to NPWT application, frequency of dressing changes, duration of NPWT, level of subatmospheric pressure used in each case, number of hospital days, complications arising from NPWT use. The outcome was favorable in all cases without such complications as infection or bleeding, a perilesional erythema (contact dermatitis caused by the used adhesive tape) being noted in only 13.51% of cases. The average duration of NPWT was 8.1 days. The frequency of dressing changes was in most cases of 3 days (89.18%) with a group mean of 3.05 days, and the average applied negative pressure was -110.83 mmHg, range -90mmHg to -120 mm Hg. No complications requiring the interruption of NPWT use were recorded. NPWT, by stimulating wound constriction and granulation tissue formation is an option in the management of acute or chronic wounds of various etiologies, whether infected or not, resulting in a decrease in the number of surgeries and their complexity, length of hospital stay and, last but not least, reduced patient suffering.

Keywords: negative pressure wound therapy, Vacuum Assisted Closure, subatmospheric pressure, oncological abdominal surgery, perilesional erythema, granulation tissue

Negative pressure wound therapy (NPWT) is known as a non-invasive technique that uses a device that generates a subatmospheric pressure [1] ranging from 50 to 150 mm Hg. Pressure can be generated continuously or intermittently [2], thus causing drainage of wound secretions, improved tissue perfusion, thus helping to heal the tissue defect by wound contraction and stimulation of granulation tissue proliferation [4-6]. In *1979*, a *suction* and *irrigation system* for the *treatment* of *wounds* was *described* in *Russia.* Then, in Germany, in 1992, a negative pressure system was used for the treatment of exposed fractures. Argenta and Morykwas [7] have validated NPWT in an animal model (pig) so that to later use it humans. The use of NPWT expanded over time, Joseph et al. and McCallon et al. demonstrating its efficiency [8, 9]. Numerous studies conducted over time have demonstrated the usefulness of this therapeutic solution in the treatment of wounds of various etiologies. The European Wound Management Association (EWMA) identified a total of 3287 publications published from 1990 to 2015. As a result, indications for use of negative pressure therapy have expanded beyond the number of 100 situations in which it can and should be used [10]. NPWT is used to treat soft tissue defects of various etiologies: vascular surgery, digestive surgery, thoracic surgery, spinal surgery, burns, infections etc. The aim of this study was to demonstrate the efficacy of NPWT by reference to several variables such as the type of lesion, affected anatomical region, sex and age of patients, interventions prior to placement of NPWT device, frequency of dressing changes, the used negative pressure level, length of hospital stay, and adverse reactions.

Experimental part

The study group included 37 patients. The study patients received treatment between January 2014 and December 2017. All patients with acute lesions have initially received surgical treatment for primary surgical toilet as well as reconstruction of affected elements: osteosynthesis (trauma to the lower leg and hand bones, tenorrhaphies and myorrhaphies (trauma to the upper limb), incision with evacuation of purulent collections followed by daily lavage for 3-4 days in case of septic arthritis of the fist, necrectomy and lavage in the case of catheter-related thrombophlebytis.

Prior to negative pressure therapy, chronic lesions benefited from wound debridement and lavage, with a slight bleeding of the NPWT location area. The lavage of the area of NPWT device placement was performed in all cases with hydrogen peroxide, followed by betadine and physiological saline solution (table 1).

NPWT was applied using continuous suction from a VAC device or from hospital's centralized suction system. Subatmospheric pressure varied depending on the anatomical region and patient tolerance ranging from -90 mm Hg to -120 mm Hg, and the frequency of dressing changes ranged from 3 to 4 days. In all cases polyurethane foam was used. In the cases presenting microbial flora while using NPWT, targeted systemic antibiotic therapy was also used.

Patients were assessed and monitored by laboratory investigations (blood, wound secretions), and the appearance and size of wounds at each dressing change was documented by photographs, direct measurements,

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Table 1

CASE DISTRIBUTION ACCORDING TO TREATMENT

No	NUMBER OF CASES	ETIOLOGY	LOCATION	SEX	DIAGNOSTIC	TREATMENT
1.	2	iatrogenically	dorsal hand	F	Thrombophlebitis of the catheter	Necrectomy+NPWT+STSG (split-thickness skin graft)
2.	11	posttraumatic	upper limb	7M+4F	Soft tissue defects dorsum of the hand / fist / forearm backside	Necrectomy+NPWT+STSG/ local flap
3.	7	chronic diseases	lower leg	5M+2F	Trophic leg ulcers +diabetes	Necrectomy+NPWT+STSG
4.	5	posttraumatic	lower leg	4M+1F	Soft tissue defects	Necrectomy+NPWT+STSG/ local flap
5.	3	posttraumatic (fracture) + infection	wrist	1M+1F	Septic arthritis of the wrist	Incision + drain + Lavage + NPWT+STSG
6.	1	digestive oncology surgery	right iliac fossa	F	Adenocarcinoma mucinous right colon with invasion in the abdominal wal	Reconstruction with component separation technique and omental flap+ NPWT+STSG
7.	1	digestive oncology surgery	anterior abdominal wall (evisceration blocked	F	Upper rectal neoplasm	Debridement+NPWT+Secondary suture
8.	1	digestive oncology surgery	left iliac fossa	F	Serous ovarian carcinoma extended in abd	Necrectomy+ advancement flaps + NPWT+ secondary suture
9.	1	breast cancer surgery	antero-lateral thoracic wall	F	Breast cancerlocally advanced	Necrectomy+ advancement flaps + NPWT+ secondary suture
10.	3	digestive oncology surgery	inguinal region	M	Inguinal lymphadenectomy secondary malignant melanoma	Necrectomy+NPWT+STSG
11.	1	oncological thoracic surgery	toraco-dorsal wall	M	Liposarcoma thoracic posterior	Necrectomy+ advancement flaps + NPWT+ STSG
12.	1	digestive oncology surgery	left iliac fossa	M	Parastomal collection	Necrectomy+ advancement flaps + NPWT+directed epithelization

Table 2

LABORATORY INVESTIGATIONS AND THE APPEARANCE AND SIZE OF WOUNDS OF THE MONITORED PATIENTS

	AGE	SEX	DIAGNOSIS	ASSOCIATED DISEASES	PREVIOUS TREATMENT	NPWT USAGE TIME (DAYS)	FREQUENCY OF CHANGING DRESSINGS (DAYS)	THE VALUE OF THE NEGATIVE PRESSURE USED (MMHG)	HOSPITALIZATION TIME (DAYS)	SIDE EFFECTS	ASSOCIATED INFECTIONS
1	64	F	Catheter thrombophlebitis dorsal right hand with extensive cutaneous necrosis	HTA, cardiac insufficiency cls II, Diabetes	excision venous cord + necrectomy	7	3	100	10	none	+
2	56	F	Catheter thrombophlebitis dorsal right hand with extensive cutaneous necrosis	HTA	necrectomy	5	3	110	12	erythema, stinging	+
3	48	M	Trophic leg ulcers	Diabetes	the wounded lavage + degranulation	8	3	120	14	none	+
4	72	M	Trophic leg ulcers	HTA, Diabetes	the wounded lavage + degranulation	8	3	120	13	none	+
5	65	M	Trophic leg ulcers	heart disease	the wounded lavage + degranulation	7	3	120	15	none	+
6	70	M	Trophic leg ulcers	heart disease	the wounded lavage + degranulation	6	3	120	14	none	+
7	59	M	Trophic leg ulcers	Diabetes,obesity	the wounded lavage + degranulation	8	3	110	16	none	+
8	70	F	Trophic leg ulcers	Diabetes,obesity	the wounded lavage + degranulation	8	3	100	20	none none	+
9	74	F	Trophic leg ulcers	Diabetes,obesity	the wounded lavage + degranulation	7	3	90	14	none	+
10	26	M	Comminuted fracture calcaneus bone exposurea	none	osteosynthesis	10	3	110	14	none	-
11	36	M	Bimaleolar fracture with partial soft defect	none	osteosynthesis	9	3	120	14	none	-
12	42	M	Open leg fracture with soft tissue defect	none	osteosynthesis	8	3	110	14	erythema,	-

13	35	M	Dog bite 1/3 distal external leg soft tissue defect	none	wounded lavage +necrectomy	8	3	100	12	none	+
14	45	F	Open leg fracture with soft tissue defect	HTA	osteosynthesis	10	3	120	16	none	-
15	69	M	Septic arthritis punch	heart disease	incision + lavage	12	3	110	21	none	+
16	72	F	Septic arthritis punch	chronic ischemic cardiopathy, HTA, Diabetes	incision + lavage	10	3	110	20	none	+
17	40	M	1/3 medium leg open fracture soft tissue defect	none	osteosynthesis + necrectomy	8	3	120	12	nicuna	-
18	56	M	Crushing trauma to the dorsal hand with soft tissue defect (exposure tendon and bone)	none	the wounded lavage	8	3	110	13	nicuna	-
19	42	M	Trauma by circular hand with open fractures and fault pati MC 2-4 soft dorsal hand	none	wounded lavage + osteosynthesis	8	3	110	12	none	-
20	36	M	Wound bitten hand (horse) 1/3 average forearm with soft parts defects	none	wounded lavage	6	2	120	10	none	+
21	28	M	Complex (circular) hand trauma with soft defects	none	wounded lavage + osteosynthesis + primary tenoraphy	8	3	110	16	none	-
22	49	M	Wound bitten hand (dog) face forearm with faulty soft parts	HTA + Diabetes	wounded lavage + mioraphy	6	3	100	10	none	-
23	32	M	Crush trauma.,Compartment Syndrome+ soft forearm defects	none	wounded lavage + decompression incisions + necrectomy	8	3	110	18	none	-
24	57	M	Electrocuted hand	Hepatic disease	wounded lavage + necrectomy	6	3	110	10	none	-
25	52	F	Road accident, Volar forearm soft tissue defect front	none	wounded lavage+ STSG ()	6	3	120	10	none	-
26	74	F	Wound bitten hand (cat) neglected old infected	HTA + chronic ischemic cardiopathy,	the wounded toilet + necrectomy	6	3	120	15	none	+
27	67	F	Road accident, soft tissue dorsal forearm	HTA	the wounded toilet + STSG	6	3	120	10	erythema	-
28	55	F	Open fracture (both bones) of the forearm with faulty soft parts	none	the wounded toilet + osteosynthesis +tenorafie + STSG	6	3	120	10	erythema	
29	38	F	Adenocarcinoma mucinous right colon with invasion in the anterior abdominal wall and ms psoas right	none	right hemicolectomy + excision of abdominal wall and psoas muscle; abdominal wall reconstruction with component separation technique and omental flap (cutaneous defect of 8/10cm)	13	4	100	27	None	-
30	86	F	Upper rectal neoplasm	HTA, chronic ischemic cardiopathy, , obesity Scar tissue granulomas pubo-supraombilical - Multiple excision of post N colon operated	rectus anterior resection with total mesorectal excision and colorectal anastomosis evisceration blocked	8	4	100	26	erythema	+
31	67	F	Serous ovarian carcinoma high grade (G3), bilateral locally advanced	HTA, diabetes	total hysterectomy with bilateral anexectomy + pelvic lymphadenectomy, omentectomy, segmental enterectomy with entero-entero-anastomosis + Hartmann op Necrectomy + advancing flaps	9	3	120	24	None	+
32	59	F	Breast cancer, locally advanced (necrotic, suprainfected)	HTA, diabetes	modified radical mastectomy type Madden (flap necrosis) Necrectomy + avancement flaps	9	3	120	40	None	+

33	72	M	Melanoma malign gamma - op, Adenopathic inguinal block	HTA, chronic ischemic cardiopathy	inguinal lymphadenectomy (flap necrosis) Necrectomy+ STSG (split-thickness skin graft)	6	3	90	16	None	-
34	58	M	Melanoma malign gamma - op, Adenopathic inguinal block	none	inguinal lymphadenectomy (flap necrosis) Necrectomy+ STSG(split-thickness skin graft)	8	4	120	21	eryth ema	-
35	63	M	Melanoma malign gamma - op, Adenopathic inguinal block	HTA	inguinal lymphadenectomy (flap necrosis) Necrectomy+ STSG(split-thickness skin graft)	6	3	100	18	None	-
36	45	M	Scapular liposarcomamultiple operated and relapsed	none	flaw reduction with forward flaps + STSG(split-thickness skin graft)	6	3	120	6	None	-
37	70	M	collection parastomala	HTA, diabetes	necrectomy + advancing flaps	10	3	100	12	None	+

and microbiological assessment of secretions collected from wounds (table 2).

Our study was done in accordance with the Ethical Committee regulations and in accordance to some published models [11].

Results and discussions

Our study included a series of 37 patients, 24 men and 13 women, with posttraumatic and chronic soft tissue defects of different etiologies and locations. The mean age of the 37 patients enrolled in the study was 55.37 years, range 26 - 86 years (fig. 1).

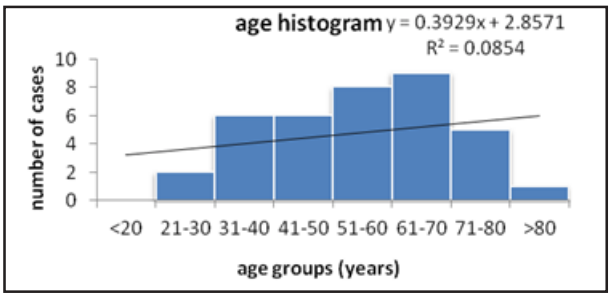

Fig. 1. Age histogram (N = 37)

Gender distribution showed a predominance of male patients (62.16%) with an M: F ratio of 1.64 (fig. 2).

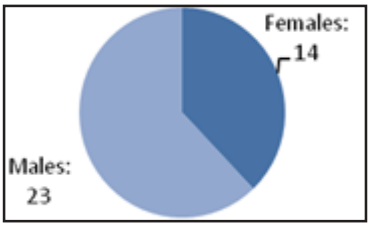

Fig. 2. Gender distribution

Patients in the study group belonged to the following diagnostic groups: catheter-related thrombophlebitis (2 cases - 5.41%), septic wrist arthritis (2 cases - 5.41%), trophic ulcer of the lower leg (7 cases - 18.91%), open fractures of limbs (5 cases - 13.51%), bite wounds (3 cases - 8.11%), injury (traffic accidents, crushing, industrial tools, total 8 cases - 18.91%), oncologic surgery (7 cases -18.91%) of which digestive surgery - 2 cases, breast and chest surgery - 2 cases, malignant melanoma - 3 cases, others (electrocution, liposarcoma, parastomal collection - 1 case each) (fig. 3).

The patients of this study presented the following associated diseases: arterial hypertension (15 cases), diabetes mellitus (11 cases), chronic heart diseases (8 cases), obesity (4 cases), other (liver disease - 2 cases).

Treatments previous NPWT were: necrectomy - 13 cases (35.13%), primary surgical debridement - 11 cases (29.72%), osteosynthesis - 8 cases (21.62%), surgical toilet and degranulation - 7 cases (18.91%), split-thickness skin graft (STSG) – 7 cases (18.91%), advancement flaps - 4 cases (10.81%), flap necrosis - 4 cases (10.81%) and others. The mean duration of NPWT was 7.78 days, range 5 -13 days. The mean duration of NPWT for the 4 patients undergoing digestive, breast, and chest surgery and for all oncological patients was 9.75 days and 8.1 days, respectively. In cases where NPWT was used after free split-thickness skin graft, the average duration of NPWT was 6.5 days (fig. 4).

The frequency of dressing changes was in most cases (89.18%) of 3 days with a group mean of 3.05 days. The negative pressure level averaged -110.83 mmHg, range – 90 mmHg to – 120 mmHg. The average length of hospital stay was 15.47 days, range 6-40 days (table 3).

Adverse reactions occurred in only 6 patients (16.21%), represented by a simple perilesional erythema. We performed the ANOVA Regression (95% CI) for the following variables: duration of NPWT and the level of the

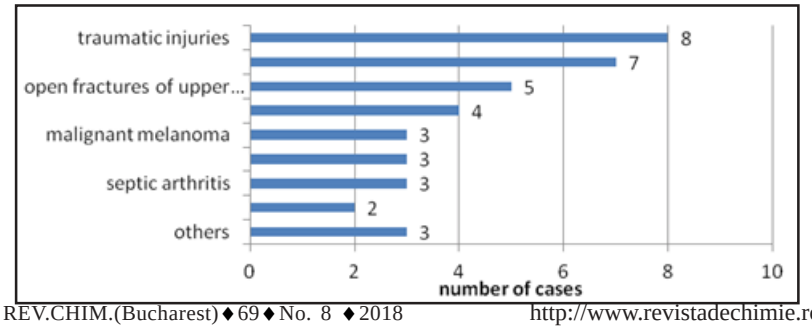

Fig. 3. Diagnostic groups

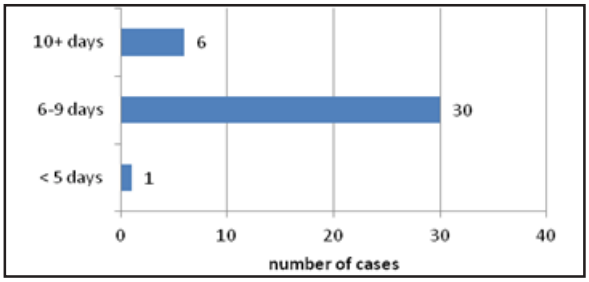

Fig. 4. Mean duration of use for NPWT

Variables / Descriptive statistics	Mean	Minimum	Maximum
Age	55.37	26	86
Length of use for NPWT (days)	7.78	5	13
Frequency of NPWT change (days)	3.05	2	4
Value of negative pressure (mmHg)	110.83	90	120
Length of stay (days)	15.47	6	40

Table 3
DESCRIPTIVE STATISTICS OF THE MONITORED PATIENTS

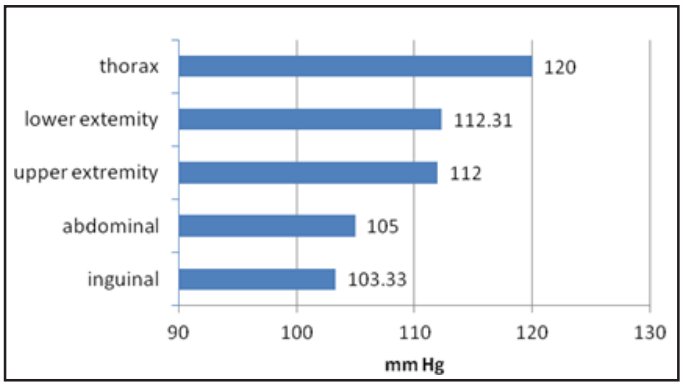

Fig. 5. Mean values of negative pressures used in patients depending on the lesions sites

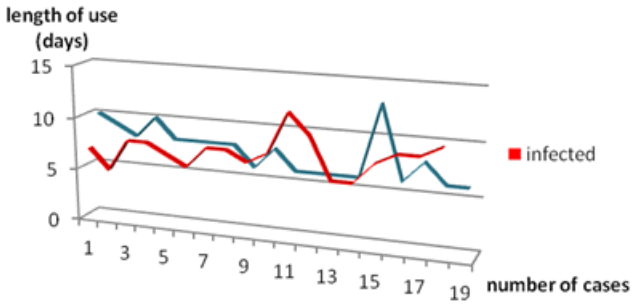

Fig. 6. Length of use of NPWT compared in lesions with *versus* without associated infections

used negative pressure which showed a correlation coefficient = 0.1253 (weak correlation) for p = 0.45 (significance F = 0.45, alpha = 0.05), with no statistical significance (N = 37). Regarding age and duration of NPWT, r = 0.1575 (weak correlation) was obtained, and for p = 0.35 (significance F = 0.35), without statistical significance.

Applying ANOVA Regression for age and negative pressure level we obtained r = 0.2067 (weak to moderate correlation), for p = 0.21 (significance F = 0.21), with no statistical significance, and for age and length of hospital stay r = 0.2243 (weak to moderate correlation), for p = 0.18 (significance F = 0.18), with no statistical significance. Taking into account the length of hospital stay and duration of NPWT, the correlation coefficient r = 0.5277 represents a good moderate correlation and for p = 0.007 (significance F = 0.007) with high statistically significance. The level of negative pressure used in the study patients ranged from -90 to -120 mmHg. By comparing the average pressure levels, it was noted that for inguinal (-103.33 mmHg) and abdominal (-105 mmHg) locations, lower pressures than for upper limb (-112 mmHg) and lower limb locations (-112.31 mmHg) were needed (fig. 5).

By calculating the mean duration of NPWT, it was found that it was of 7.88 days in the group of patients with infected wounds (N = 18), greater than the 7.68 days in the group of patients without wound-associated infections (N = 19) (fig. 6).

The principles of negative pressure applied to wounds to accelerate healing date back to the eighteenth century when the fluids, toxins, and microorganisms from wounds were suctioned with the help of dome-shaped glass cups, heated and applied to the wound, where passive cooling brings about a negative pressure [12].

The mechanism of action of NPWT is based on the mechanical effects represented by the physical forces that determine a biochemical response at the cellular level [13, 14]. Mechanical stress induced by NPWT results in

increased production of extracellular matrix components such as elastin, proteoglycans, collagen and glycosaminoglycans [15-17]. Important in NPWT is the decrease in edema. The application of *NPWT* may *reduce edema.* Edema, by increasing the pressure in the microcirculation, leads to a decrease in oxygen and nutrient intake at cellular level, as well as in the ability to protect against infections. Studies have demonstrated a reduction in edema by negative pressure therapy used in patients with burns to both hands [1, 7, 18]. Subatmospheric pressure acts on wound edges causing wound contraction and stimulating granulation tissue proliferation [1,7,19]. There are two forms of negative pressure therapy: continuous and discontinuous or intermittent [20]. In this study we used only continuous pressure ranging from - 90 mm Hg to - 120 mm Hg. The value of the subatmospheric pressure used to obtain the best results is below -125 mm Hg [10]. Today there is a large variety of devices used in negative pressure therapy. Most of them are portable so as to ensure greater independence of the patient with the possibility of mobilization during treatment. When portable devices are not available, hospital wall suction systems can be used to apply negative pressure, as we did in some cases. Materials used to cover injuries when negative pressure is used are foams or gauzes with different properties related to pore size and stability. Selecting the type of wound filler material influences the healing process [21]. The first material used in 1988 for NPWT was PVA foam with a pore size of 60 - 1,500 μm. Today, black polyurethane foam with pore size range from 400 - 600 μm is the most widely used material, also used in our study [22]. Studies have shown that dressing should be changed every 2 to 4 days, but there are no fixed intervals [23]. In the majority of our cases the dressings were changed at 3-day intervals (one case at 2-day and three at 4-day intervals). Shweiki et al. reported an interval of 1.7-4.1 days between dressings as safe and useful [24]. NPWT has the advantage of less frequent dressing changes and thus less pain associated with dressing changes; also repeated surgical interventions are avoided and the techniques used are of lesser complexity, usually of the type of free split-thickness skin plasties or neighboring flaps [25]. There are also situations where in the absence of any technical possibility to reconstruct a limb segment due to the general state of the patient NPWT is a technical solution where by a possible amputation of a member can be avoided. *NPWT devices have* now become *even smaller* and are available for *single-use* (PICO), thus enhancing patient comfort [26]. The only discomfort experienced when using negative pressure therapy is patient perceived pain when the device is installed and possibly at subsequent dressing changes. Complications are rare when complying with the guidelines for the use of NPWT [27]. Similar applications were found to be effective also in other interventional fields, especially in the conservative therapy of gastrointestinal fistulas [28]. Not the least, potential concomitant diseases and conditions of patients should be carefully analyzed, as a vast group of disorders causing capillary failure, microvessel abnormalities or subsequent infections could influence the rate of wound healing despite proper therapy appliance [29-31].

Conclusions

NPWT is simple and safe technique, easy to use, with no complications when it is correctly indicated. It can be used in patients with associated comorbidities, who cannot benefit from complex surgeries due to poor general health. Subatmospheric pressure used is adapted to patient tolerance and to anatomical region. NPWT stimulates the contraction of the wound edges and granulation tissue formation, making easier the subsequent reconstruction.

References

1.MORYKWAS, M.J., ARGENTA, C., SHELTON-BROWN, E.I., McGUIRT, W., Ann. Plast. Surg., **38**, no. 6, 1997, p. 553.

2.FUJITANI, T., ZENKE, Y., SHINONE, M., MENUKI, K., FUKUMOTO, K., SAKAI, A., J. UOEH, **37**, 2015, p. 185.

3.LIU, D.S.H., SOFIADELLIS, F., ASHTON, M., MACGILL, K., WEBB, A., Injury, **43**, no. 6, 2012, p. 772.

4.WEBB, L.X., J. Am. Acad. Orthop. Surg., **10**, no. 5, 2002, p. 303.

5.MORYKWAS, M.J., FALER, B.J., PEARCE D.J., ARGENTA, L.C., Ann. Plast. Surg., **47**, no. 5, 2001, p. 547.

6.HYLDIG, N., BIRKE-SORENSEN, H., KRUSE, M., Br. J. Surg., **103**, no. 5, 2016, p. 477.

7.ARGENTA, L.C., MORYKWAS M.J.M., Ann. Plast. Surg., **38**, no. 6, 1997, p. 563.

8.JOSEPH, E., HAMORI, C.A., BERGMAN, S., ROAF, E., SWANN, N.F., ANASTASI, G.W., Wounds, **12**, 2000, p. 60.

9.McCALLON, S.K., KNIGHT, C.A., VALIULUS, J.P., CUNNINGHAM, M.W., McCULLOCH, J.M., FARINAS, L.P., Ostomy Wound Manage., **46,** 2000, p. 28.

10.APELQVIST, J., WILLY, C., FAGERDAHL, A.M., FRACCALVIERI, M., MALMSJO, M., PIAGGESI, A., PROBST, A., VOWDEN, P., J. Wound Care, **26** (Sup3), 2017, p. 1.

11.AGHEORGHIESEI CORODEANU, D.T., POROCH, V., 6th LUMEN International Conference on Rethinking Social Action Core Values, 16-19 April 2015, Iasi, Romania, Rethinking Social Action. Core Values, p. 33

12.HARRIS, T., Medical Examiner, **1,** 1838, p. 250.

13.SAXENA, V., HWANG, C.W., HUANG, S., EICHBAUM, Q., INGBER, D., ORGILL, D.P., Plast. Reconstr. Surg., **114** , no. 5, 2004, p. 1086.

14.INGBER, D. E., PRUSTY, D., SUN, Z. et al., J. Biomech., **28**, 1995, p. 1471.

15.WILKES, R., ZHAO, Y., KIEWETTER, K., HARIDAS, B., J. Biomech. Eng., **131**, no. 3, 2009, p. 031012.

16.LABLER, L., RANCAN, M., MICA, L. et al., J. Trauma Inj. Infect. Crit. Care, **66**, no. 3, 2009, p. 749.

17.BAUDOUIN-LEGROS, M., PAQUET, J.L., BRUNELLE, G., MEYER, P., J. Hypertens., **7**, 1989, p. 114.

18.KAIRINOS, N., SOLOMONS, M., HUDSON, D.A., Plast. Reconstr. Surg., **123**, no. 2, 2009, p. 589.

19.FALABELLA, A.F., CARSON, P., EAGLSTEIN, W.H., FALANGA, V., J. Am. Acad. Dermatol., **39,** no. 5, 1998, p. 737.

20.MAURYA, S., BHANDARI, P.S., Adv. Wound Care, **5**, 2016, p. 379.

21.YOUNG, S.R., HAMPTON, S., MARTIN, R., Int. Wound J., **10**, no. 4, 2013, p. 383.

22.FRACCALVIERI, M., SCALISE, A., RUKA, E. et al., Eur. J. Plast. Surg., **37**, no. 8, 2014, p. 411.

23.HUANG, C., LEAVITT, T., BAYER, L.R., ORGILL, D.P., Curr. Probl. Surg., **51,** no. 7, 2014, p. 301.

24.SHWEIKI, E., GALLAGHER, K. E., Int. Wound J. , **10**, no. 1, 2013, p. 13.

25.CIUNTU, B.M., VASILUTA, C., NEGRU, R., HULTOANA, R., CIUNTU, R., GEORGESCU, S.O., SIRBU, P.D., AZOICAI, D., Rev. Chim.,(Bucharest), **68**, no.7, 2017, p. 1648.

26.PAYNE, C., EDWARDS, D., Eplasty, **28,** no.14, 2014, p. 20.

27.CIUNTU, B.M., VASILUTA, C., ANTON, N., CIUNTU, R., DAMIAN, M., CIUMAGHEL, A., BLAJ, M., AZOICAI, D., GEORGESCU, S.O., Rev. Chim., (Bucharest), **68**, no. 8 , 2017, p. 1923.
28.CONSTANTINESCU, G., SANDRU, V., ILIE, M., NEDELCU, C., TINCU, R., POPA, B., J Gastrointestin Liver Dis, **25**, no. 2, 2016, p. 249.
29.TOADER, E., BAHRIN, L.G., SANDU, I., BIRSA, M.L., REZUS, C., Rev. Chim. (Bucharest), **67,** no. 7, 2016, p. 1394.
30.BRANISTEANU, D.E., PINTILIE, A., ANDRES, L.E., DIMITRIU, A., OANTA, A., STOLERIU, G., BRANISTEANU, D.C., Medical-Surgical Journal-Revista Medico-Chirurgicala, **120** no. 4, 2016, p. 760.
31.REZUS, E., CONSTANTIN, M.M.L., REZUS, C., Rev. Chim. (Bucharest), **66,** no. 7, 2015, p. 1015.

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