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Updates of Closed-incision Negative Pressure Therapy (CINPT) Review

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Abstract – The idea of negative pressure strategy traces all the way back to the earliest civilizations; during the Roman period, the method of utilizing dom-shapped cupping glasses was utilized to make the pull expected to promote recuperating. This procedure was utilized all through the nineteenth century. In 1821, an English doctor named Dr. Francis Fox imagined the "glass leech" strategy. From that point in 1952, an imaginative methodology was acquainted with the treatment of serious, complex wounds using sub-atmospheric or negative pressure known as "negative pressure wound therapy" (NPWT). Afterward, the "vacuum-assisted closure", or VAC treatment system established by Dr. Louis Argenta in 1990 changed the advanced wound care market, nevertheless the most clinically proven alternative for the treatment of complex, difficult to-heal wounds. These treatments use a foam dressing that is adjusted to the wound bed. Whenever fixed and put under negative (vacuum) pressure, the system establishes a remarkable wound healing environment that has been displayed to advance the wound healing process, decrease oedema, set up the wound bed for closure, promote the development of granulation tissue and remove infectious materials. The negative pressure treatment system tends to addresses personal satisfaction through a simple to-utilize system intended to help surgeons in the management and treatment of comorbid wounds, and open abdomen and other wound complications to assist with accomplishing primary fascial closure. Comorbidities can be defined as a simultaneousness of multiple chronic diseases in a same patient. Closed-incision negative tension treatment (CINPT) has changed the manner by which caregivers treat the most serious, complex wounds or comorbid wounds. Wound healing can be accomplished by the host's innate and adaptive immune mechanisms as in an uninfected simple surgical incision through the skin or by combination of the host's defence mechanisms and therapeutic modalities. It has been affirmed in some clinical investigates that growth factors apply astonishing consequences for wound-healing promotion and skin function restoration with no obvious complications. In this review, we have focusing on the treatment of wound complications secondary to comorbidity by a mix of negative pressure treatment followed by a positive pressure infusion with growth factor concentrates.

Keywords – Wounds And Injuries, Negative Pressure, Equipment And Supplies, Growth Factor Concentrates, Positive Pressure.

I. INTRODUCTION

Wound healing is a complex and dynamic physiological process that includes different cells, mediators, extracellular matrix (ECM) parts, growth factors, and proteinases [1]. It requires recruitment and differentiation of progenitor/stem cells into tissue-committed somatic cells. Stem cells differentiation is managed by intrinsic factors and extrinsic micro-environmental cues. On the contrary, infection initiates an immuno-inflammatory reaction and tissue destruction, which hinders the capability of tissue regeneration [2].

Recuperating of wound comprises of three stages including inflammatory, proliferative, and re-epithelialization stages. Frequently, the inflammatory stage endures two to five days after skin damage. Quickly haemostasis is started by intravascular platelets, a clot is formed and bleeding is arrested. Platelets are activated by thrombin and release a several growth factors, for example, epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factors (TGF-α and TGF-β),

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insulin-like growth factor-1 (IGF-1), platelet-determined growth factor (PDGF), etc. These growth factors diffuse into the wound tissue, serving as biological signals to attract leukocytes, monocytes, macrophages, and neutrophils, which further mediate inflammation. For the most part, the proliferative stage requires three days to about fourteen days after injury, promoting cell proliferation and migration. Proangiogenic factors like PDGF released by platelets and inflammatory cells inside the wound region promote new blood vessels and capillaries. The migration of fibroblasts is furthermore inspired at the same time with angiogenesis by the stimulation of PDGF and FGF from inflammatory cells, forming granulation tissue. ECM composed of collagen, proteoglycans, and elastin is created with the expansion of fibroblasts. Myofibroblasts assume a part in the compression of the injury region after some of the fibroblasts differentiate into myofibroblasts. Activated keratinocytes around the wound edge relocate to the injured region to complete re-epithelialization. Re-epithelialization differs from three weeks to two years' post-wound. Collagen III in newly synthesised ECM is slowly replaced by collagen I and it organizes and expand the elasticity of recuperated skin. This stage additionally involves scar formulation. [1]

Complete recovery without a scar, following injury in humans, can happen just in the pre-natal foetus within 24 weeks of growth. Post-natal wounds generally recuperate by heal or by a combination of repair and regeneration. Some lower vertebrates, like the salamander and zebrafish, have a wonderful ability to regenerate whole appendages, the lens of eyes, and portions of the heart. [2]

1. Pathophysiology

The skin is a laminated structure, involving (from superficial to deep) the epidermis, dermis, and hypodermis, which is likewise alluded to as the subcutaneous or fatty tissue layer. The epidermis is additionally subdivided into (from superficial to deep) layer corneum, layer lucidum, layer granulosum, layer spinosum, and stratum basale. Each layer has its exceptional structure and cellular composition, adding to its characteristic function within the epidermis. [7] These microscopic processes, thusly, add to the microscopic processes engaged with the consistent daily maintenance of skin, including wound recuperating.

Wound healing Is divided into acute and chronic stages. An acute injury to the skin at first actuates a proinflammatory cascade comprising haemostasis followed by inflammation. This includes neutrophils and various cytokines and happens over the initial seven days after the injury. The inflammation then slowly starts to settle into the proliferative and re-epithelialization periods of wound recuperating. This begins with angiogenesis and reinnervation including endothelial cells and fibroblasts, which leads to the cardinal component of wound recuperating: the development of healthy granulation tissue. [8]

As granulation tissue shapes, a shift towards the final phase of wound recuperating happens, known as the remodelling stage, to re-establish the epithelium of the skin. This stage can keep going for anywhere between 12 to 24months and includes collagen deposition, interceded by growth factors, for example, fibroblast growth factor and epidermal growth factor, to shape a cross-linked matrix. [9,10]

Contrastingly, a chronic wound involves a skin lesion that has failed to recuperate within the normal timescale of a normal wound. It is imagined that stasis in the inflammatory phase of wound recuperating is the most common characteristic of these wounds and demonstrates a frank dysregulation of normal processes. Typically, there is a causative proponent, for example, repetitive tissue stress or an ongoing inflammatory trigger, for example, microbial infection. [11]

The archetypical pathological processes involved in chronic wounds involves protease-induced extracellular matrix destruction, penetration of proinflammatory cytokines, and attended growth factor signalling. This, in combination with excessive fibrous tissue deposition, like collagen and fibronectin, eventually makes a vicious circle that propagates the inflammation and prevents any progression to the proliferative phase. The principal microscopic findings in chronic wound tissue are macrophages, excessive granulation tissue, and fibrosis. At last, this prompts excessive scar formation and poor skin compliance.

NPWT aims to improve the physiology engaged with wound healing through different processes, many of which have so far just been studied in an in-vitro labatory setting. In any case, the known principal mechanisms are macro-deformation, micro-deformation, excess fluid removal, and equilibration of the wound microenvironment. It is valuable to see the value in the mechanism of action of NPWT as a continuum of numerous contributory factors rather than independent, hypothetical occurrences.

First, wound shrinkage is brought about by directly applying 125 mmHg of sub-atmospheric pressure to the foam. This mechanical process is called macro-deformation, which can apparently reduce the wound space by approximately 80%. Second, suction through the pores in the foam invokes mechanical pressure to the wound surface, which causes microscopic ripples to the

wound edge because of expanded tissue tension. This process is known as microscopic deformation and promotes normal cellular proliferation, migration, differentiation, and angiogenesis due to induced hypoxia causing the release of vascular endothelial growth factors. Third, the negative pressure directly transport excess inflammatory exudate away from the wound site, alleviating wound bed tissue compression and assisting with re-establishing microvascular circulation. Ultimately, eliminating excess extracellular fluid helps a normal oncotic and osmotic pressure gradient through the extrication of excess proteins and electrolytes. Other adjunctive processes include expanded endothelial and epithelial cell migration, as well as keratinocytes. Notwithstanding the thermal insulation of the wound managed by the sealed NPWT dressing, this multitude of individual mechanisms apply positive outcomes on the wound tissue and encourage healthy tissue formation to propagate normal wound healing. [12]

2. Indications

Negative pressure wound therapy is essentially used to treat complex injuries which are non-healing or in risk of non-recuperating. These can be comprehensively categorized into acute and chronic wounds. NPWT is indicated for acute wounds when the wound can't be closed by primary intension because of the risk of infection, active infection, or swelling. [13]

Traumatic wounds, for example, open fractures or open lacerations are the absolute most regularly noticed acute wounds. Other traumatic wounds can incorporate degloving wounds (traumatic injuries that results in the top layers of skin and tissue being torn away from the underlying muscle, connective tissue or bone) and burns, which cause partial thickness skin loss. Most of these wounds are at high risk of infection because of infection from exposure to the surrounding environment. Primary closure or skin grafting of such a wound in the acute setting would basically entrap the microorganisms in the soft tissue and lead to abscess formation. Furthermore, retention of devitalized tissue would prompt necrosis and further tissue loss. Subsequently, the effective adjunctive utilization of NPWT depends on a surgical debridement and wash out of the wound to advance healthy granulation tissue and encourage wound apposition.

NPWT would likewise be indicated for dehisced wounds, which can be acute or chronic wounds and often refractory to primary closure. This is on the grounds that NPWT gives an interim measure to protect wound bed and empower the resuscitation of the skin, which accordingly expands the possibilities of subsequent successful wound closure. Additionally, NPWT can assist with cultivate a healthy wound bed to enhance the effective take-up of a skin graft for same reasons. Extra indications incorporate skin breakdown because of ulceration secondary to numerous aetiologies and closed wounds, for example, surgical incisions, including skin flaps and grafts. [14]

3. Contraindications

A careful wound assessment should be completed prior to applying negative pressure wound therapy to guarantee no harm to the patient is incurred. For example, any exposed vasculature or organ surfaces ought to promptly preclude the utilization of NPWT because of the serious risk of exsanguination secondary to erosive surfaces. Non-enteric and unexplored fistulae are additionally contraindicated because of a similar mechanism of excessive fluid extraction which can prompt dehydration and electrolyte imbalance. [12]

Any necrotic tissue or eschar present in the wound bed, such as, in full-thickness burns, can exacerbate non-recuperating and risk the further spread of necrosis. If either of these issues is recognized, the wound requires further intervention or an alternative dressing should be considered. The presence of underlying malignancy also contraindicates the utilization of NPWT because of the hypothetical possibility of tumour propagation and metastasis. [15] This ought to consequently be treated before the use of NPWT. Additionally, active osteomyelitis ought to ideally be treated before NPWT use, in spite of the fact that there have been instances depicted in the literature where this has not been the case without causing any further damage to the wound. [16]

The following equipment is required:

1. Alcoholic chlorhexidine (2% chlorhexidine in 70% isopropyl liquor) or betadine (7.5% povidone-iodine) preparation.
2. Sterile drapes.
3. Sterile little fragment orthopaedic surgical instrument tray OR sterile standard wound care surgical instrument tray.
4. 0.9% sodium chloride x 3 to 6 litres.

5. Sterile gauze.
6. Non-paraffinized, coated polyester net
7. NPWT pack:

a. Specialized negative pressure adhesive dressing (closed wounds)

b. Specialized pre-cut or unprepared foam dressing (open wounds)

c. Transparent adhesive sealant tape.

d. NPWT suction device.

All medical personnel can carry out negative pressure wound therapy, including doctors, nurses, and physicians' assistants. Notwithstanding, specific training and an adequate degree of expertise should be acquired before the independent application of any NPWT dressings. This is because of the complex nature of the wounds, which might be refractory to different strategies for wound management and thusly prone to further complications in the event that the process is performed incorrectly.

Closed wounds are usually dressed either on a ward or clinic via by trained healthcare personnel. Assuming the closed wounds results from a surgically closed incision or a skin graft, the initial NPWT ought to be applied in the operating room (OR) by the operating surgeon or surgical scrub nurse. Then again, open wounds warrant surgical management at the first stage in the OR. In like manner, one to two surgeons and an experienced surgical scrub nurse will be necessary all through the procedure. When the initial management in the OR has been finished, resulting NPWT dressing changes can be performed on the ward or in a clinic based environment by trained healthcare personnel. In complex poly-trauma cases, an intensive care facility might be thought of.

4. Preparation

Closed wounds can be managed inside or outside the OR, depending upon the nature of the wound. The equipment is prepared in a sterile field. The wound site is cleaned with an alcoholic chlorhexidine preparation (if not currently surgically prepared in the OR) and allowed to air dry before the NPWT dressing. Open wounds expect admittance to the OR for initial management and consequently require the pre-operative completion of a written consent form alongside with patient safety chick lists. The consent process ought to incorporate a conversation about the indications, benefits, and risks of the technique, with a confirmation to fit each risk to the individual patient as per the Montgomery standards of consent. The equipment is prepared in a sterile field in the OR by the surgical scrub nurse. [17]

The open wound is first sterilized utilizing alcoholic chlorhexidine and afterward surrounded by a sterile field involving sterile drapes according to standard surgical preparation protocols. When a sterile field has been established, the wound bed itself requires cautious preparation prior to applying the VAC device. This is on the grounds that any necrotic or infected tissue which remains will impair wound healing through the compromised blood supply and colonization of bacteria. Exhaustive debridement of infected or necrotic tissue ought to be done (just demonstrated at the first application of the VAC device except if further necrosis is distinguished), followed by a washout of the wound with a copious volume of 0.9% sodium chloride. Following wound bed preparation, the wound ought to be dried with sterile gauze and protected with a sterile, atraumatic, non-adhesive wound layer. Current practice inclines toward a non-paraffinized, coated polyester net. [18]

5. Procedure

The patient ought to be positioned to appropriately expose wound site while preserving their dignity. Closed wounds are covered with a specific adhesive dressing, the edges of which are reinforced with wide portions of transparent adhesive sealant tape to make a firm, air-tight seal around the dressing. This is the single most fundamental part of any of the NPWT, as without a sufficient seal, the sub-atmospheric pressure can't be accomplished, and treatment won't be delivered. Open wounds are covered with a specific porous foam dressing, which is cut by hand to the exact dimensions of the wound except if it is accessible in a pre-cut formulation. The foam dressing should cover the entire wound, preferably in a solitary piece; assuming the injury is too enormous, different pieces might be used to acquire satisfactory inclusion. It is crucial for report the quantity of pieces used, as this is significant for while the dressing is changed to try not to hold any pieces of foam inside the wound bed.

The foam dressing is covered thus by large strips of transparent adhesive sealant tape to make a firm, air-tight seal around the foam dressing. Dependent upon the VAC system to hand, a suction drain tube is either positioned over the foam dressing prior to applying the transparent adhesive sealant tape or applied as a part of a separate adhesive dressing which is put on top of the transparent adhesive sealant tape. Upon completion of the wound dressing, the NPWT suction device ought to be connected to the suction drain tube to test effective treatment delivery, which is demonstrated by an electronic signal on the suction device.

6. Complications

Beside complications brought about by the contraindicated utilization of NPWT, the most common complications related with NPWT are pain, bleeding, infection, and foam retention, which, thusly, can cause an infection. A common mechanical complication is unsuccessful therapy delivery because of loss of suction. This can be because of a several potential causes. The most frequent cause is an insufficient seal around the wound dressing, by which the transparent adhesive sealant tape has either been misapplied or has come off because of poor contact with the underlying skin. This ought to be helped as soon as possible to keep away from any delay in the delivery of treatment. Other causes can be the incorrect position of the suction drain tube, blockage of the suction drain tube, or a full NPWT suction device.

Other complications can incorporate a hypersensitivity response to the dressing materials, further damage to the wound through negative pressure erosion or necrosis, and intra-operative complications, for example, damage to surrounding nerves, veins, and soft tissue. Assuming skin breakdown happens or there is localized pain around the site of the negative pressure, topical emollient therapy can be utilized, or an alternative non-adherent dressing can be applied under the transparent adhesive sealant tape to decrease skin tension. Assuming any staining or duskiness of the wound bed or wound edges are recognized, then should ought initially to be decreased. If this continues or deteriorates, the device ought to be switched off. It is likewise critical to stay cautious for dehydration secondary to extracellular fluid loss through the NPWT suction drain. Intravenous maintenance fluid ought to be considered to alleviate this risk. [12]

7. Clinical Importance

Whenever performed accurately by trained healthcare professionals, negative pressure wound therapy is a high yield, adjunctive therapy for managing complex wounds, bringing about improved wound healing and restoration of dermal integrity in affected patients. It has widespread clinical applications across a group of specialities, including vascular, orthopaedic, and plastic surgery, along with dermatology, endocrinology, and tissue viability. The type of wound included determines the length of therapy and the intended healing process; along these lines, it can differ significantly between patients. [12]

8. Upgrading Medical Care Team Results

Negative pressure wound therapy forms a cornerstone of advanced wound care and shows magnificent utility for complex acute and chronic wounds. In any case, this procedure should be completed accurately by suitably trained personnel for optimal efficacy. Members from the healthcare team who wish to use NPWT should acquire the appropriate knowledge before applying negative pressure wound therapy and be familiar with the anatomy, physiology, indications, and contraindications related with this wound care modality. One of the many benefits of NPWT is that once adequate skill is accomplished, this type of wound care can be executed by multiple healthcare members, including doctors, nurses, nurse practitioners, and physicians' assistants. An admonition to this is that this procedure is completed by the operating surgeon when performed in the operating room. Nonetheless, it is vital to consider that this procedure in itself requires a multidisciplinary approach, with the anaesthesiologist, surgical scrub nurse, and operating room practitioners all providing respective expertise. At last, as referenced previously, NPWT can be used by various specialities, including dermatology, plastic surgery, trauma, orthopaedic surgery, general surgery, vascular surgery, and endocrinology. Accordingly, it is basic to consider the more extensive healthcare team with this process and how every member decidedly means for patient care. Good communication and an appreciation for each team members can essentially enhance patient care. [12]

II. Technical Report

Masden et al. concentrated on that there is a significant rate of postoperative infection and dehiscence in patients with numerous comorbidities. [19] Surgical site infection and other common surgical site complications (dehiscence, hematoma, and seroma formation) can cause serious and frequently life-threatening complications. Gauze adhesive dressings, and skin adhesives have

traditionally been used for incision management. In any case, negative pressure wound therapy (NPWT) over clean, closed surgical incisions (closed negative pressure therapy [CINPT]) has turned into a new choice for incision management. [20]

NPWT highlights a positive outcome on open and complicated wounds. A growing body of the literature has revealed the benefits of NPWT over closed incisions to help to reduce complications in high-risk groups. Subsequently, it has been utilized for "at –risk surgical incisions" determined to redistributing lateral tension and holding incision edges together. There is little comparative evidence for the utilization of CINPT in acute incisions of general or colorectal surgical patients viewed as at high risk of wound complications secondary to comorbidity. CINPT might lessen the risk of external wound contamination, since the dressing is sealed and applied in a sterile environment. [21]

The prevalence of people experiencing chronic wounds has risen sharply, because of the dramatically increasing frequency of obesity and chronic diseases like diabetes and venous and arterial insufficiency. Chronic wounds influence around 2% of European and US populations; for instance, the prevalence of diabetic ulcers alone has already reached as high as 10%-22% in diabetic patients. In any case, traditional therapies generally involve costly and long lasting treatments with a high ulcer relapses rate of above 70%. [22]

NPWT has generally been utilized to acute or chronic open wounds through such mechanisms as protection of the wound bed, splinting of soft tissues, decrease of edema, increased perfusion, and enhanced formation of granulation tissue. [21] Vacuum-assessed closure (VAC) treatment uses an open-cell polymer foam dressing that is adjusted to the wound bed. There is consensus that intact skin should not be exposed to polyurethane foam on the grounds that the foam can excoriate and blister the tissue. [23] A non-adherent layer is recommended between the foam and the incision. Typically, CINPT dressings do not need to be changed all through the seven-day span of therapy. The decreased frequency of dressing change is particularly advantageous in obese patients or in patients with difficult to access incisions to-get. [21]

Various experimental studies are being directed to cause-effect relationship between the mechanical signals and the transduction pathways that outcome in an improved granulation reaction. A three-layered finite element model was developed by Wilkes et al. to measure the tissue micro-deformations during therapy. This was utilized to study on the effect of the dressing type and negative pressure level on varieties in the micro-deformational strain fields in an artificial dermal wound bed. [24]

A definitive objective of wound management is to prevent serious infection, accelerate wound healing, and reduce scars and pain for patients. Repair and regeneration is managed by cell-to-cell and cell-to-extracellular matrix cross-talk and by the expression of growth factors/cytokines and other bioactive molecules at different temporal and spatial stages during wound healing. Topical therapeutic agents contain growth factors and antimicrobial agents, being crucial for the wound therapy and skin regeneration. [25]

1. Positive pressure infusion

Comorbid wounds are usually deficient in large numbers of the required adjuvants for physiological wound healing. In this way, these adjuvants should be transported to the wound site. One of the methods to provide them is through infusion. An infusion system might be a device, and any associated disposables, delivering fluids or medications in solution for the patient. A fluid reservoir keeps the infusate for delivery by a positive pressure displacement pump. Infusate is drawn by the pump into a drugs pressurant chamber. A check valve prevent backflow to the reservoir. [26]

As a general rule, infusion devices can be partitioned into two main groups: the gravity flow infusion devices and infusion pump. A gravity flow infusion device depends on the gravitational force applied by a liquid column to push the fluid through a venous access into the patient's blood stream, whereas infusion pump has a motorized pumping mechanism to create the positive pressure. Within the gravitation gathering are the manual gravity flow sets and the infusion controllers. [27]

There are several types of disposable infusion pumps, including elastomeric, positive pressure (spring powered and gas pressure powered), negative pressure (vacuum), etc.

1.1 Elastomeric Infusion pumps

In all elastomeric disposable devices, the pressure on the fluid is produced by the force of a stretched elastomer.

1.2 Spring-powered infusion/Positive pressure Spring-powered pumps

These are powered by the energy stored in a compressed spring, the flow rate being fundamentally higher at the beginning of infusion than at the end. These varieties are due to fluctuations in the pressure applied on the fluids by the compressed spring; the pressure decreases with diminishes in the volume of the drug reservoir.

2- Negative Pressure infusion pumps

With negative pressure pumps, a driving force is produced from the pressure force across two sides of the pump's low-pressure chamber wall, with one side being at extremely low pressure (inside a vacuum chamber) and another being at atmospheric environment. [26]

3- Infusion Pump System with Controls

Duran et al. presented an infusion pump system in which the serum amount is controlled and delivery of the required amount of serum to the patient is guaranteed. The system is planned as to close itself when the serum flow amount reaches the predetermined limit value, and planned as to give an audible warning when a problem occurs within this process. [27]

The accuracy of each pump's flow relies upon a several factors, including temperature, fluid viscosity, atmospheric pressure, back pressure, incomplete filling, and storage. Regarding the atmospheric pressure, albeit the driving systems of spring and balloon pumps are not straightforwardly subject to atmospheric pressure for their operation, their flow accuracy can be significantly impacted by changes in surrounding pressure. Negative pressure devices are typically impacted by varieties in the atmospheric pressure. Disposable infusion pumps can be utilized in many areas, including home care, patient-controlled analgesia, patient-controlled epidural analgesia, continuous peripheral analgesia, continuous epidural analgesia, continuous IV analgesia and paediatric applications. The pressure created by disposable pumps on fluid is 250-600 torr, compared to 5-1200 torr of pressure for electric pumps. [26]

4- Positive pressure infusion with growth factor concentrate and updates wound management

The population with comorbidities varies from that with individual chronic diseases. The interaction between multiple conditions results about the need for a comprehensive and multidisciplinary approach and consistent continuing care [28]. Growth factors are biological active polypeptides that regulate cell growth, differentiation, and migration and apply an effect on all stages of wound healing. Some clinical researchers affirm that growth factors apply amazing impacts on wound healing promotion and skin function restoration free from side effects. [22] For the stimulated tissue repair, platelet- derived fractions have been utilized as an autologous source of growth factors and biomolecules, to be specific, platelet rich plasma (PRP), platelet poor plasma (PPP), and platelet rich fibrin (PRF). The continuous release of growth factors from these concentrates has been proposed to induce angiogenesis both in vitro and in vivo. [29] Previously, PRP was utilized to seal incisions. In plastic surgery PRP has arisen as an effective therapy adjuvant for cutaneous wounds and fat grafts. An eye-shaped PRF clot has been utilized for the surgical repair of corneal perforation. The standard surgical threads could be bio-activated with genetically modified microalgae to release both oxygen, and recombinant growth factors directly into the wound site. Challenges of utilizing exogenous growth factors is that the levels of matrix metalloproteinase are upregulated that hinder wound healing by degrading growth factors. [30]

In this way autologous growth factors focuses like PRP, PRF, etc. might be preferred to exogenous growth factors. PRP showed higher blood perfusion in the lesion as well as a more mature granulation tissue when compared with those treated with PPP. Injection of these agents within the injured muscle tissue of mice induced the reperfusion of blood into the lesion. [29] Therapeutic cerebral angiogenesis, using angiogenic factors to reinforce collateral vessel formation within the central nervous system (CNS), might be an expected strategy for cerebral revascularization. A previous dose study established that the intracerebro-ventricular infusion of vascular endothelial growth factor (VEGF) increments vascular density with minimal associated brain edema at a concentration of 5 μg/ml. [31] It was found that titanium-prepared PRP (TPRP) has better angiogenic potential over its counterpart. These novel growth factor concentrates might be additionally studied for their impacts on wound healing and their administration might be incorporated in CINPT. [32]

III. NOVEL SPECULATION

Since normal physiological wound healing is challenging to accomplish in comorbid wounds because of the disparity in necessary moleculars, a supporting infusion system should be presented. CINPT dressings needn't bother with to be changed all through the

seven-day length of treatment, and reports recommend that the decreased frequency of dressing change is particularly advantageous in obese patients. Since the proliferative phase of wound healing generally requires three days to about fourteen days after incision, highlighted with cell proliferation and migration [22], a positive infusion pressure with growth factor concentrate (PPIGFc) will be required in this phase of wound healing.

A positive pressure pump can manage the inflow of growth factor concentrates depending on the requirement of each individual patient. Accordingly, we can infer that three to seven days of CINPT can be followed by one to about fourteen days of PPIGFc for wound complications secondary to comorbidity. This allows a continuous flow of preferably “autologous" growth factors through the foam dressing, into the wound depths and inaccessible areas. By PPIGFc, the steady cells can be stimulated into the labile cells and enter the cell growth cycle, in this way supporting faster healing.

1- Few adjuvants in wound healing

The topical utilization of EGF promotes cell proliferation, differentiation, and migration and accelerates epidermal regeneration. The topical utilization of PDGF increases the structural integrity of vessels and promotes cell proliferation, ECM deposition and re-epithelialization. The typical/subcutaneous infusion of granulocyte-macrophage colony –stimulating factor(GM-CSF) promotes the local recruitment of inflammatory cells, and stimulate cell proliferation and differentiation and wound contraction. The topical utilization of basic fibroblast growth factor (bFGF) promotes collagenase production, ECM deposition and re-epithelialization. The topical utilization of TGF-β promotes granulation tissue formation, re-epithelialization, matrix formation, and remodelling. [22]

The topical administration of growth factors after debridement is a favourable approach to strengthen wound healing because of the cell deficiency or a noticeable deterioration of quality in chronic wounds. PDGF is the only recombinant growth factor approved by the FDA in USA for topical application and is utilized for the therapy of diabetic foot ulcers (however over dosages are reported to have an increased risk of disease). VEGF-A improves re-epithelization of diabetic foot wounds associated with improved vessel formation. EGF increases healing of skin grafts following partial thickness burns. Studies conducted on mice recommended TGF-α in early re-epithelization. FGF-10 has been successful in increasing the healing rate of non-healing venous ulcers. [30]

The utilization of hydrosol/scaffold like titanium dioxide (TiO2) strongly inhibits the growth of Staphylococcus aureus and induces red blood cell aggregation to stop bleeding. As indicated by a report by Fan et al., a Nano fibrous scaffold carrying nano-TiO2 hydrosol was designed for better skin repair. [33] Because of the embedding of nano-TiO2, the scaffold strongly inhibited the growth of S. aureus and induced red blood aggregation to stop bleeding. Collagen-chitosan (COL-CS) porous scaffolds have been broadly utilized as a dermal analogue to induce fibroblast infiltration and dermal regeneration. To improve an anti-bacterial properties, nano-TiO2 hydrosol was introduced into COL-CS scaffolds. TiO2/COL-CS porous scaffolds were fabricated through a freeze-drying process, and scanning microscopy (SEM) was utilized to observe the micro- structure of the scaffolds. Fourier transform infrared spectroscopy (FT-IR) decided the intermolecular interactions within the scaffolds. The outcomes showed that the scaffolds are nearly more porous and it might give a moist climate to wound repairing. The degradation in the lysozyme solution for four weeks showed that porous scaffolds are steady, which can satisfy the wound coverage protection within the repair period. [33]

Injectable Nano-engineered hydrogels enhance cell adhesion and spreading, increment platelet binding, diminish blood clotting time, and facilitate in vitro tissue regeneration and wound healing. Chitosan and (polyethylene oxide) are electrospun into Nano fibrous meshes as mimics of ECM. Nanofiber/nanoparticle scaffolds significantly accelerate tissue regeneration and remodelling and promotes angiogenesis. These adjuvants might have to hasten wound healing when utilized in combination with CINPT, but the therapeutic protocols are yet to be studied. [22]

2- Impacts of pressure differences on wound healing

Liu et al. compared effects of negative pressure and positive pressure in wound healing by making a homemade device. They found that negative pressure and positive pressure promote an inflammatory reaction and upregulated the expression of growth factors, for example, EGF, VEGF, PDGF, TGF-β1. Both negative pressure and positive pressure significantly expanded cell proliferation in the wound tissue on day 10 compared with the controls. They estimated the number of endothelial cells in wound tissue by platelet endothelial cell adhesion molecule 1-CD31-positive staining. Positive pressure expanded the number of CD31-

positive cells more significantly than the negative pressure in the wound tissue from days 3 to 10. A lower amount of mesenchymal stem cells in the wound tissue was identified following exposure to negative pressure in wound healing when compared with positive pressure therapy. [34]

within the presence of soluble mitogens, whereas retracted cells stay quiescent. It had been theorized that the use of micromechanical forces to wounds can promote wound healing through cell shape-dependant, mechanical control component. A stimulated VAC application was created to study the impacts of vacuum-induced material deformation and it was concluded that the tissue deformity stretches individual cells accordingly promoting proliferation in the wound microenvironment. Utilization of micromechanical forces could likewise be a helpful technique to stimulate wound healing through the promotion of cellular division, angiogenesis a native elaboration of growth factors. [35]

3- Advances of positive pressure infusion/Nano-drug delivery system

Gillies et al. developed a positive pressure infusion for the clinical method for accomplishing convection-enhanced delivery of therapeutic agents within the tissues of the CNS for the treatment of glioblastoma multiform and other diseases of the brain. [36] Regardless of tremendous advances in drug therapy, the utilization of nanotechnology-based systems has changed the field of drug delivery, offering the likelihood to deliver therapeutic agents to local areas in the brain. [37]

Chronic wounds stay a challenge because current therapies generally fail to give ideal results in wound healing. The Nano-drug delivery systems (DDSs) has brought a new knowledge into skin regeneration of wounds. These drugs carriers prolong drug release, protect drug from degradation, and improve skin retention. They have huge potential in preventing of drug degradation and sustaining drug release. Nano-DDSs carrying therapeutic agents are being considered and manufactured, chiefly including liposomes, polymeric nanoparticles, inorganic nanoparticles, lipid nanoparticles, Nano fibrous structures, and Nano hydrogel. [22]

4- Molecular events in wound healing

Chronic medical conditions are significantly more predominant among older adults [28]

As far as possible is how much times that an ordinary cell population divides before it quits dividing. Each time a cell divides, the length of telomeres is shortened attributable to the loss of pieces of telomeres. Whenever the length of telomeres becomes shortened to a critical point, the cell is prevented from dividing. This is called replicative senescence. [25] In the cell growth cycle, stable cells are not cycling nor dying. They can be induced to re-emerge the cycle by an appropriate stimulus. Despite the fact that growth can be achieved by shortening the cell cycle, and so on, the main factors are those that recruit stable cells into the cell cycle. Polypeptide growth factors present in the serum or produced by cells are the most important factors. Cell growth is started by the binding of a putative growth factors to specific receptors either in the cell or outside the cell. Most growth factor receptors are outfitted with intrinsic protein tyrosine kinase activities that are activated after ligand binding. Such receptors have an enormous glycosylated extra-cell ligand binding domain, a single hydrophobic transmembrane region, and a cytoplasmic domain that contains the tyrosine kinase activity. Ligand binding prompts a conformational adjustment of the extra-cell domain, which thus actuates dimerization of receptors. The net outcome is the actuation of a protein phosphorylation cascade that stimulates the stable cells to re-enter the cell growth cycle. [38]

IV. Conclusion

Certain comorbid conditions are known to expand the risk of surgical wound complications. Comorbid patients typically have a deficient immune system that prompts a deficient repair system. In such patients, a combination of CINPT and positive pressure infusion with autologous growth factor concentrates (PPIGFc) is theoretically supported. There is a differing beneficial impact of mechanisms depending on the type of wound. [39]

This furnishes the tissues with growth factors consequently compensating their lack. The strategy can be effectively finished by separating the negative pressure tube and substituting it with the tube of a positive pressure infusion of growth factor concentrates. In this manner, it isn't required that the dressing should be changed and the rate of infusion can be regulated by any of the types of pumps as is expected by the state of the patient. The protocol can be CINPT followed by PPIGFc, vacuuming away the by-products of inflammation and inhibiting bacterial growth and then bathing the wound area with a constant supply of growth factors accordingly stimulating the stable cells to begin regeneration. Albeit further researchers should be implicated, a

combination of CINPT, for supporting wound closure, and PPIGFc, for revascularisation of the surgical site, may support the better management of postoperative infection and dehiscence in patients with multiple comorbidities.

Table 1. Mechanisms of NPWT depending on the type of wound

Wound type	**Proposed mechanism**
Acute open wounds	Increased perfusion; granulation stimulation
Closed surgical incisions	Exudate management
Chronic wounds	Removal of corrosive substances
Wounds closed by skin grafts and skin substitutes	Exudate management; granulation stimulation; stabilisation of graft/substitute

ABBREVIATIONS

(NPWT): "negative pressure wound therapy"

(VAC): "vacuum-assisted closure"

(CINPT): Closed-incision negative tension treatment

(ECM): extracellular matrix

(EGF): epidermal growth factor

(FGF): fibroblast growth factor

(TGF-α and TGF-β): transforming growth factors

(IGF-1): insulin-like growth factor-1

(PDGF): platelet-determined growth factor

(PRP): platelet rich plasma

(PPP): platelet poor plasma

(PRF): platelet rich fibrin (PRF)

(GM-CSF): granulocyte-macrophage colony –stimulating factor(GM-CSF)

(bFGF): basic fibroblast growth factor

(TiO2): titanium dioxide

(COL-CS): Collagen-chitosan

(SEM): scanning microscopy

(FT-IR): Fourier transform infrared spectroscopy

(DDSs): drug delivery systems

(PPIGFc): autologous growth factor concentrates (PPIGFc)

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

AUTHORS CONTRIBUTION

Authors have equally participated and shared every item of the work.

REFERENCES

[1] Danino, A. M., and E. Coeugniet. "Letters to the editor: negative pressure dressing: some background to a monopole business." *Eplasty* 8 (2008).

[2] Argenta, Louis C., and Michael J. Morykwas. "Vacuum-assisted closure: a new method for wound control and treatment: clinical experience." *Annals of plastic surgery* 38 (1997): 563-577.

[3] Shakespeare, P. G., et al. "The Journal of Continuing Professional Development."

[4] Scalise, Alessandro, et al. "Improving wound healing and preventing surgical site complications of closed surgical incisions: a possible role of incisional negative pressure wound therapy. A systematic review of the literature." *International wound journal* 13.6 (2016): 1260-1281.

[5] Norman, Gill, et al. "Negative pressure wound therapy for surgical wounds healing by primary closure." *Cochrane Database of Systematic Reviews* 6 (2020).

[6] Kim, Paul J., et al. "Negative pressure wound therapy with instillation: review of evidence and recommendations." *Wounds* 27.12 (2015): S2-S19.

[7] Brown, Thomas M., and Karthik Krishnamurthy. "Histology, dermis." *StatPearls [Internet]*. StatPearls Publishing, 2021.

[8] Almadani, Yasser H., et al. "Wound healing: A comprehensive review." *Seminars in Plastic Surgery*. Thieme Medical Publishers, Inc., 2021.

[9] Jones, Ruth Ellen, Deshka S. Foster, and Michael T. Longaker. "Management of chronic wounds—2018." *Jama*320.14 (2018): 1481-1482.

[10] Ousey, Karen, Alan A. Rogers, and Mark G. Rippon. "Hydro-responsive wound dressings simplify TIME wound management framework." *British Journal of Community Nursing* 21. Sup12 (2016): S39-S49.

[11] Castiglione, F. "Stem Cell and Stromal Vascular Fraction Treatment for Penile Tunica Albuginea and Urethral Fibrosis." (2019).

[12] Bayer, Lauren R. "Negative-pressure wound therapy." *Interventional treatment of wounds*. Springer, Cham, 2018. 193-213.

[13] Mosti, G. "Wound care in venous ulcers." *Phlebology*28.1_suppl (2013): 79-85.

[14] Daryago, Adi Agung Anantawijaya, et al. "Management of diabetic foot ulcers: dermatology perspective."

[15] Pflibsen, Lacey R., et al. "Negative pressure wound therapy in malignancy: always an absolute contraindication?." *Plastic and Reconstructive Surgery–Global Open* 8.8 (2020): e3007.

[16] Obolensky, V. N., and D. V. Zolotarev. "Methods of prolonged local antibiotic therapy and topical negative pressure in the treatment of infectious wound complications sternotomy: analytical review, clinical examples."

[17] Chan, Sarah W., et al. "Montgomery and informed consent: where are we now?." *Bmj* 357 (2017).

[18] David, Franck, et al. "A randomised, controlled, non-inferiority trial comparing the performance of a soft silicone-coated wound contact layer (Mepitel One) with a lipidocolloid wound contact layer (UrgoTul) in the treatment of acute wounds." *International Wound Journal* 15.1 (2018): 159-169.

[19] Masden, Derek, et al. "Negative pressure wound therapy for at-risk surgical closures in patients with multiple comorbidities: a prospective randomized controlled study." *Annals of surgery*255.6 (2012): 1043-1047.

[20] Fernandez, Luis G., et al. "Closed incision negative pressure therapy: review of the literature." *Cureus* 11.7 (2019).

[21] Roos, Elin, Christian Toso, and Jeremy Meyer. "Comment on “Meta-analysis, Meta-regression, and GRADE Assessment of Randomized and Nonrandomized Studies of Incisional Negative Pressure Wound Therapy Versus Control Dressings for the Prevention of Postoperative Wound Complications”." *Annals of Surgery* 274.6 (2021): e698-e699.

[22] Wang, Wei, et al. "Nano-drug delivery systems in wound treatment and skin regeneration." *Journal of nanobiotechnology* 17.1 (2019): 1-15.

[23] Karlakki, S., et al. "Negative pressure wound therapy for management of the surgical incision in orthopaedic surgery: a review of evidence and mechanisms for an emerging indication." *Bone & joint research* 2.12 (2013): 276-284.

[24] Wilkes, R1, et al. "Effects of dressing type on 3D tissue microdeformations during negative pressure wound therapy: a computational study." (2009): 031012.

[25] Lin, L. M., and P. A. Rosenberg. "Repair and regeneration in endodontics." *International endodontic journal* 44.10 (2011): 889-906.

[26] Lin, L. M., and P. A. Rosenberg. "Repair and regeneration in endodontics." *International endodontic journal* 44.10 (2011): 889-906.

[27] Gomez, Treesa W., Justus W. Gomez, and Rajesh Gopal. "Clinical Applications and Benefits of Using Closed-Incision Negative Pressure Therapy for Incision and Surrounding Soft Tissue Management: A Novel Approach for Comorbid Wounds." *Cureus* 12.7 (2020).

[28] Jaul, Efraim, et al. "An overview of co-morbidities and the development of pressure ulcers among older adults." *BMC geriatrics* 18.1 (2018): 1-11.

[29] Martínez, Constanza E., Patricio C. Smith, and Veronica A. Palma Alvarado. "The influence of platelet-derived products on angiogenesis and tissue repair: a concise update." *Frontiers in physiology* 6 (2015): 290.

[30] Yamakawa, Sho, and Kenji Hayashida. "Advances in surgical applications of growth factors for wound healing." *Burns & trauma* 7 (2019).

[31] Ennis, Steven R., et al. "Effects of intraventricular infusion of vascular endothelial growth factor on cerebral blood flow, edema, and infarct volume." (2003).

[32] Strauss, Franz-Josef, et al. "Effect of platelet-rich fibrin on cell proliferation, migration, differentiation, inflammation, and osteoclastogenesis: a systematic review of in vitro studies." *Clinical oral investigations* 24.2 (2020): 569-584.

[33] Kumar, Aishwari S., and Kaladhar Kamalasanan. "Drug delivery to optimize angiogenesis imbalance in keloid: a review." *Journal of Controlled Release* 329 (2021): 1066-1076.

[34] Liu, Jinyan, et al. "Homemade-device-induced negative pressure promotes wound healing more efficiently than VSD-induced positive pressure by regulating inflammation, proliferation and remodeling." *International Journal of Molecular Medicine* 39.4 (2017): 879-888.

[35] Saxena, Vishal, et al. "Vacuum-assisted closure: microdeformations of wounds and cell proliferation." *Plastic and reconstructive surgery* 114.5 (2004): 1086-1096.

[36] Gillies, George T., et al. "Positive pressure infusion of therapeutic agents into brain tissues: mathematical and experimental simulations." *Technology and Health Care* 13.4 (2005): 235-243.

[37] Fakhoury, Marc. "Drug delivery approaches for the treatment of glioblastoma multiforme." *Artificial cells, nanomedicine, and biotechnology* 44.6 (2016): 1365-1373.

[38] Carlson, Nathan E., and Robert B. Roach Jr. "Platelet-rich plasma: clinical applications in dentistry." *The Journal of the American Dental Association* 133.10 (2002): 1383-1386.

[39] Argenta, Louis C., and Michael J. Morykwas. "Vacuum-assisted closure: a new method for wound control and treatment: clinical experience." *Annals of plastic surgery* 38 (1997): 563-577.