Systematic review of the negative pressure wound therapy in kidney transplant recipients

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Abstract

AIM
To review negative pressure wound therapy (NPWT) as an important addition to the conventional methods of wound management.

METHODS
A systematic review, performed by searching the PubMed, EMBASE and Cochrane Library databases, showed 11 case reports comprising a total of 22 kidney transplantation (KT) patients (range, 1 to 9), who were treated with NPWT. Application of NPWT was associated with successful healing of wounds, leg ulcer, lymphocele and urine leak from ileal conduit.

RESULTS
No complications related to NPWT were reported. However, there was paucity of robust data on the effectiveness of NPWT in KT recipients; therefore, prospective studies assessing its safety and efficacy of NPWT and randomised trials comparing the effectiveness of NPWT with alternative modalities of wound management in KT recipients is recommended.

CONCLUSION
Negative pressure incision management system, NPWT with instillation and endoscopic vacuum-assisted closure system are in investigational stage.

Key words: Negative pressure; Wound therapy; Kidney transplantation; Wound infection; Wound dehiscence

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Core tip: Systematic review of the safety and efficacy of negative pressure wound therapy (NPWT) in kidney transplant (KT) recipients revealed 11 case reports, which have shown the effective role NPWT in the management of wound dehiscence, lymphocele, urine leak from ileal conduits and leg ulcers. Because of the lack of robust evidence on the safety and efficacy of NPWT in KT patients, prospective multicentre studies recruiting large number of patients is recommended to examine the role
of NPWT in the treatment of wound-related complications in KT recipients. The efficacy of negative pressure incision management system, NPWT with instillation and endoscopic vacuum-assisted closure system remain in investigational stage.

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INTRODUCTION

Kidney transplantation (KT) represents the best treatment modality for patients with end-stage renal disease, providing the best outcomes for survival, quality of life and cost-effectiveness[1]. Immunosuppressive agents administered to prevent rejection and prolong transplant survival, not only increase susceptibility to infections, but also delay wound healing. Post-operative wound infection leading to cavitation and dehiscence continue to remain serious problems resulting in extended hospital stay, readmissions, repeated surgical interventions and protracted recovery, thereby imposing extra cost to the healthcare delivery system[2]. The wound complication rate after KT ranges between 2% to 47%. The risk factors for these complications are advancing age, diabetes mellitus, body mass index, kidney failure, type of surgical incision, re-operation, operator’s experience, and immunosuppressive drugs including sirolimus and steroids[3-6]. The wound-related complications can present as superficial infection, haematomas, lymphocele, and immunosuppressive drugs including sirolimus and steroids[7]. The wound-related complications can present as superficial infection, haematomas, lymphocele, and full-thickness wound dehiscence leading to incisional hernias[7].

Negative pressure wound therapy (NPWT), also referred to as, vacuum-assisted closure therapy (VACT), topical negative pressure therapy or microdeformational wound therapy has been evaluated over last two decades and is considered as an useful adjunct to the management of diverse range of lesions including open abdominal wounds, open fractures, post-traumatic wounds, split-thickness skin grafts and after clean surgery in obese patients[8-13]. Application of any new form of treatment in KT patients is associated with concerns on the part of clinicians, particularly when robust evidence supporting their safety and efficacy are lacking. A systematic review of the published literature was carried out to evaluate the effectiveness and safety of NPWT in KT recipients presenting with wound-related complications.

MATERIALS AND METHODS

Literature search

A systematic electronic literature search was performed in PubMed, EMBASE and Cochrane Library databases from inception to March 2016. The search terms “renal transplantation”, “kidney transplantation”, “negative pressure wound therapy”, “vacuum-assisted closure”, “wound”, and “topical negative pressure therapy” were used. EndNote software (Version X7.5, BLD 9325; Thomson Reuters, Philadelphia, PA, United States) was used to compile pertinent references.

Renal transplantation technique

KT is performed by using classical Gibson’s muscle-cutting incision, where the iliac vessels and urinary bladder are accessed extraperitoneally. The renal vessels are anastomosed to the iliac vessels and the ureter to the bladder by the techniques described previously[14]. Wound infection leading to muscular dehiscence exposes the kidney to the external environment, which predisposes to infection around the kidney, haemorrhage from mycotic aneurysms of the vascular anastomoses, lymph leak, urine leak, and dehiscence of muscle layers leading to incisional herniation.

Principles of NPWT

The beneficial effect of negative sub-atmospheric pressure on the wound results in gradual closure of wound edges by micro- and macrodeformation of the wound surface, and by suction of infectious material and interstitial fluid, reduces tissue oedema. Decompression of tissue increases blood flow and tissue oxygenation, thereby accelerates the wound healing cascade including, angiogenesis, neurogenesis, granulation tissue formation, cellular proliferation, differentiation and migration of appropriate cellular components at the site of healing[15-20].

Glass et al[21] in a systematic review, evaluated the molecular basis for the promotion of wound healing by NPWT and observed an increase in the expression of cytokines, chemokines and growth factors, which reflected mechanoreceptor and chemoreceptor transduction in response to stress and hypoxia. There was reduction of expression of matrix metalloproteinase-1, -2, -9 and -13, with no changes on the activity of tissue inhibitor of metalloproteinase-1[21].

The NPWT device comprises of black polyurethane ether foam dressing or white polyvinyl alcohol foam, which is tailored to fit into the dimension of the wound. A tube with multiple perforations is placed within the foam for the evacuation of the wound discharge. The tube together with the foam is then covered with an occlusive drape, which helps to maintain uniform negative pressure. The effluent of the wound is collected in a canister, which is attached to the vacuum pump with an adjustable negative pressure, ranging from 50 and 125 mmHg (Figure 1A and B). At the interval 48-72 h, the soiled dressing is replaced with fresh dressing at the bedside, when progress of healing is assessed. The device can be used in preparation for secondary suture, a skin graft, flap or until full closure of the wound has taken place[22,23]. The oldest and most popular device in clinical practice is the vacuum-assisted
closure (VAC® KCI, San Antonio, Texas) system (Figure 1C and D) [24].

The contra-indications for the applications of NPWT are excessive pain with NPWT, presence of pus or excessive bleeding and intolerance. The success of NPWT is assessed by the reduction in wound size by at least 10% per week or 50% improvement over 4 wk period, which indicates high probability of success of the therapy [25].

RESULTS

The literature search identified 11 case reports comprising of a total of 22 KT patients (range, 1 to 9) (Table 1), who were treated with NPWT [26-36]. Comparison between NPWT and other methods of wound treatment in KT patients has not been reported in any study.

In 2003, Hodzic et al. [32], for the first time, reported successful outcome of application of NPWT for 15 d in 2 KT patients prior to secondary suture of wounds. Successful treatment of an infected and dehisced laparotomy wound following liver and KT in a patient by employing NPWT was reported by Zanus et al. [26], where associated complications included acute pancreatitis, abdominal compartment syndrome and wound infection by multi-drug resistant organisms. The patient required 14 successive laparotomies and NPWT for 6 mo for complete closure of the wound [26]. Similarly, Markić et al. [34] have described successful treatment with application of NPWT in 2 KT patients who developed infected and dehisced wounds. NPWT was applied for 2 and 3 wk, respectively, which was followed by secondary sutures [34].

The occurrence of ureteric complications significantly delays the recovery following KT and the incidence of such complication ranges between 1.2% and 8.9% [37]. Urinary leak rate of 11% requiring re-implantation was reported by Surange et al. [38] in a series of KT into ileal conduits. Two cases of urine leak and wound dehiscence following KT into ileal conduits were managed successfully by Heap et al. [28] with the application of NPWT. Secondary suture of the wounds was carried out after two and three months in these patients. The renal function was restored in both patients leading to 141 µmol/L and 75 µmol/L of serum creatinine, respectively, at the end of 3 mo [28]. On the other hand, Ortiz et al. [27], had negative experience of NPWT in a KT recipient with peri-renal collection and wound infection. They concluded that NPWT had encouraged and prolonged urine leak, which had healed after 5 d of discontinuation of NPWT [27]. Iesari et al. [36] had applied VAC device in a KT patient who had developed spontaneous rupture of urinary bladder due to gangrenous cystitis and extensive wound dehiscence associated with multidrug resistant Acinetobacter baumannii infection. There was significant urine leak following VAC therapy, hence this was discontinued and topical homologous platelet-rich gel was used resulting in complete wound healing [36].

Infection caused by virulent organisms after skin grafts and reconstructive surgery in KT recipients not only lead to failure of treatment, but also can be life-
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| Ref.     | Year | Country | No. of cases | No. of NPWT days | Indications                      |
|----------|------|---------|--------------|------------------|----------------------------------|
| Iesari et al. [30] | 2015 | Italy   | 1            | Not described    | Wound dehiscence                 |
| Bozkurt et al. [31] | 2015 | Turkey  | 1            | 5                | Primary surgery                   |
| Markic et al. [32] | 2014 | Croatia | 2            | 14, 21           | Wound dehiscence                  |
| Franchin et al. [33] | 2014 | Italy   | 1            | 45               | Infected lymphocele               |
| Zanus et al. [34] | 2011 | Italy   | 1            | 180              | Wound dehiscence, pancreatitis    |
| Ortiz et al. [35] | 2011 | United States | 1 | 15              | Wound infection                   |
| Heap et al. [36] | 2010 | United Kingdom | 2 | Not described | Wound dehiscence, Urine leak       |
| Theodis et al. [37] | 2009 | Greece  | 1            | Not described    | Vibrio infection of leg           |
| Devries et al. [38] | 2009 | United States | 1 | Not described | Leg wound                         |
| Shrestha et al. [39] | 2007 | United Kingdom | 9 | 3, 5, 5, 8, 10, 15, 30 | Wound dehiscence, infection |
| Hodzic et al. [40] | 2003 | Germany | 2            | 15               | Wound dehiscence                  |

NPWT: Negative pressure wound therapy.

### Discussion

All infected wounds with associated collections require surgical drainage for early healing. Fleischmann et al. [41] from Germany, in 1993, for the first time described the benefit of exposing wounds to sub-atmospheric pressure, which promoted wound debridement and healing. He applied this method in 15 patients with compound fractures and observed enhanced proliferation of the granulation tissue with no associated bone infection leading to complete healing of fractures [41]. In 1997, Louis Argenta and Michael Morykwas introduced NPWT therapy, for the first time, in the treatment of bed sores and slow healing wounds. Since then, NPWT has been extended to treat various types of wounds resulting from surgery, trauma, infection, congenital deformities and tumours [42-44]. The experience of NPWT gained over the past two decades has encouraged clinicians to treat patients globally in both hospital and domiciliary environments [44-46].

This systematic review has confirmed the available evidence on the safety and efficacy of the application of NPWT in KT recipients limited to case reports. On the other hand, the reported experiences do support NPWT in the management of complex wounds following KT, including urine leak from KT in ileal conduits and lymphoceles. The theoretical risk of haemorrhage and urine leak from transmission of suction pressure on the vascular and ureteric anastomoses cannot be ignored. Prolonged urine leak had occurred in two reported cases after KT where NPWT was applied. Discontinuation of NPWT had led to resolution of urine leak. In author’s single KT patient with a urine leak from the ureterovesical junction, treatment with NPWT led to persistence of urine leak for 1 wk. Resolution of the urine leak occurred 2 d after discontinuation of NPWT therapy. Successful outcomes of NPWT in the management of wound infections in cardiac and liver transplant recipients have been described previously [47,48].

Development of enterocutaneous fistula during the course of NPWT is always a concern, which is particularly related problems.

In a prospective study reported by Shrestha et al. [39], 9 KT patients had developed wound infection with contamination and wound dehiscence. This was associated with significant amount of discharge from the wound, which failed to respond to standard method of treatment. Treatment with NPWT for a median of 9 (range 3-30) d led to cessation of discharge from the wound. Of the 9 patients, 4 patients were managed on an outpatient with portable NPWT device, where the treatment was discontinued after a median of 5.5 (range 3-7) d. The median hospital stay since the employment of NPWT was significantly shorter (5, range 2-12 d) compared to the standard method of treatment prior to application of NPWT (11 d, range, 5-20 d; P = 0.003). The wound healed completely in all 9 cases after the therapy [39].

Recently, Bozkurt et al. [31], for the first time, employed Prevena incision management system (Kinetic Concept Inc. San Antonio, Texas, United States) to the clean closed surgical wound for 5 d after a KT and observed complete healing of the wound with no skin or device-related problems.
applicable in deep wounds after KT, where thin layer of peritoneum lies between the bowel and the foam dressing. Occurrence of enterocutaneous fistula has been observed after NPWT in open abdominal wound. However, the evidence in support of the occurrence of this complication after NPWT is weak\(^{49-51}\).

Shrestha et al\(^{30}\), in their largest reported series of 9 patients, observed benefit of NPWT on wound healing, reduced hospital stays and convenience of wound management. The management of 4 patients on an outpatient basis with the NPWT device *in situ*, was convenient to the patient and saved hospital cost significantly\(^{39}\).

**Comparison of NPWT with standard treatment modalities**

There is no data available comparing the safety and efficacy of NPWT over conventional methods of wound management in KT recipients. However, there are several randomised trials and meta-analyses, which have assessed the effectiveness of NPWT for skin grafts and surgical wound healing by primary and secondary intentions and in chronic wounds compared with several conventional treatment methods. With regards to healing of surgical wound by primary intention, the evidence for the effect of NPWT for reducing surgical site infections, time to complete healing and wound dehiscence remains unclear\(^{52}\). A Cochrane Database Systematic Review assessed the effect of NPWT for the treatment of chronic wounds in comparison with five different comparators, which did not show that NPWT significantly increased the healing rate. The trials did have methodical flaws, therefore need for better quality research was recommended\(^{53}\). Similarly, a recent Cochrane review did not show clinical effectiveness of NPWT over alginate dressings in the treatment of open infected groin wounds and a silicone dressing in the treatment of excised pilonidal sinus when they were allowed to heal by secondary intention\(^{54}\).

**NPWT with instillation**

NPWT with instillation (NPWTi) is a recent advancement, which is being assessed in the management of complicated surgical wounds. The wound is covered with normal saline (0.9%) and left for 10-20 min for diffusion to take place. Then, 2-4 h of negative pressure at -125 mmHg is applied. A panel of experts in the first International Consensus Guidelines for NPWTi have recommended its use in high risk patients with multiple comorbidities including diabetes, contaminated traumatic wounds, and wounds complicated by invasive infection or extensive biofilm. Available evidence suggest achievement of better outcomes with the addition of NPWTi to standard care in properly selected cases, compared to standard care alone\(^{55,56}\). As majority of KT patients often have associated co-morbidities, NPWTi may be an option in this group of patients.

**Negative pressure incision management**

Colli et al\(^{57}\) employed the negative pressure incision management system in clean closed incisions, for the first time, in 10 patients after cardiac surgery and observed normal wound healing in patients where complications were expected after surgery. Bozkurt et al\(^{53}\) have reported their experience of using Prevena incision management device in a KT recipient. A recent meta-analysis of NPWT for closed surgical incisions, (including 10 studies, 1311 incisions in 1089 patients) showed significant reduction in wound infection (RR = 0.54) and seroma formation (RR = 0.48), when NPWT was compared with standard care. The reduction in wound dehiscence was not significant. The numbers needed to treat were 3 (seroma), 17 (dehiscence) and 25 (infection). Due to heterogeneity between the included studies, no general recommendations could be made yet\(^{58}\). However, this device has a potential for its use in immunosuppressed and obese patients undergoing KT.

**Endoscopic vacuum-assisted closure system**

Endoscopic vacuum-assisted closure system (E-VAC) has developed as an important alternative in patients with upper gastrointestinal leaks not responding to standard endoscopic or surgical treatment procedures. Leak from oesophageal and gastric Anastomosis sites and perforations resulting from endoscopic procedures were successfully closed using the E-VAC therapy\(^{59,60}\). Application of this device in KT recipients remains to be explored.

This systematic review has shown successful healing of wounds, leg ulcer, lymphocele and urine leak from ileal conduit following application of NPWT in KT recipients and there was no report of complications associated with NPWT. However, there is lack of robust evidence on safety and efficacy of NPWT in KT patients. Based on available evidence on the application of NPWT in KT recipients, NPWT can be considered as a valuable adjunct in the management of infected and dehisced wounds following KT. The safety and efficacy of NPWT, negative pressure incision management system, NPWT with instillation and E-VAC system, and efficacy of NPWT in comparison with standard methods of wound management, need to be examined prospectively by including large number patients in multicentre studies.

**COMMENTS**

**Background**

Negative pressure wound therapy (NPWT) is a useful adjunct to the conventional methods of management of infected wounds with deep cavitation in the kidney transplant (KT) recipients. A systematic review was performed to assess the safety and efficacy of NPWT in KT recipients, which showed 11 case reports including 22 KT recipients who were treated with NPWT showing beneficial outcomes.

**Research frontiers**

There are no randomised trials comparing the safety and efficacy of NPWT with alternative modalities of wound management, hence multicentre prospective study by including large number of patients is recommended.

**Innovations and breakthroughs**

The negative pressure incision management, NPWT with instillation, and
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endoscopic vacuum-assisted closure system are the new developments in this field, which need to be applied and examined in the RT recipients.

Applications

NPWT has been applied in the treatment of abdominal wounds, leg ulcers, lymphoholes and urine leak from ileal conduit in RT recipients successfully.

Terminology

Negative pressure wound therapy (NPWT), also referred to as, vacuum-assisted closure therapy (VACT), topical negative pressure therapy (TNP T) or microdeformational wound therapy.

Peer-review

The authors made a comprehensive review on NPWT on KTx recipients. It provides useful information for clinicians.

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