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Incisional negative pressure wound therapy to reduce surgical-site infections in major limb amputations: a meta-analysis

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- *Purpose:* Incisional negative pressure wound therapy (iNPWT) has shown effectiveness in the treatment of high-risk surgical wounds. Especially patients with diabetes-induced peripheral arterial disease undergoing major limb amputation have a high intrinsic risk for post-surgical wound infections. While normal gauze wound dressings do not cause stimulation of microvasculature, iNPWT might improve wound healing and reduce wound complications. The purpose of this study was to systematically review the literature for rates of wound complications and readmissions, as well as post-surgical *30*-day mortality.
- *Methods:* We conducted a systematic review searching the Cochrane, PubMed, and Ovid databases. Inclusion criteria were the modified Coleman methodology Score >60, non-traumatic major limb amputation, and adult patients. Traumatic amputations and animal studies were excluded. Relevant articles were reviewed independently by referring to the title and abstract. In a meta-analysis, we compared 3 studies and 457 patients.
- *Results:* A significantly overall lower rate of postoperative complications is associated with usage of iNPWT (odds ratio (OR) = 0.52; 95% CI: 0.30–0.89; P = 0.02). There was no significant improvement for *30*-day mortality, when iNPWT was used (OR= 081; 95% CI: 0.46 – 1.45; P = 0.48). Nevertheless, we did not note *a* significant difference in the readmission rate or revision surgery between the two groups.
- *Conclusion:* Overall, the usage of iNPWT may reduce the risk of postoperative wound complications in major lower limb amputations but does not improve *30*-day mortality rates significantly. However, to anticipate surgical-site infection, iNPWT has shown effectiveness and thus should be used whenever applicable.

Keywords
- iNPWT
- major amputation
- wound therapy

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Introduction

Lower extremity amputation bears a high risk for post-surgical wound infections (1). Multi-morbid patients with diabetes-induced peripheral arterial disease represent the main subjects of major lower limb amputations (2). A combination of impaired blood supply and hyperglycemic states further increases the risk of surgical-site infections (3, 4). In such cases, as reported by Willy *et al.*, closed-incisional negative pressure wound therapy (iNPWT) has shown clinical effectiveness in the treatment of high-risk wounds compared to normal gauze wound dressings (5, 6, 7, 8).

We carried out a meta-analysis to validate our hypothesis that iNPWT is an effective tool for lowering the risk of wound infections in lower extremity amputation.

Methods

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (9). The study protocol was registered in PROSPERO (ID: CRD42021257983), a database listing current meta-analyses, at the beginning of our literature search.

From April 2021 to October 2021, a database search was done independently by the authors (AF and NG). Studies published until April 1, 2021, were checked for eligibility. MEDLINE, PubMed, and the Cochrane Library were searched for relevant studies reporting clinical outcomes after amputation surgery.

To calculate the risk of underlying bias, all included studies were analyzed with the ROBINS-I tool.

Search strategy

The following search strategy was applied:

('extremity amputations'[Title/Abstract] OR (amputation[Title/Abstract])) AND ((negative pressure wound therapy[Title/Abstract]) OR ('closed incision negative pressure'[Title/Abstract]) OR (inpwt[Title/Abstract]) OR (ivac[Title/Abstract]) OR ('vacuum therapy'[Title/Abstract])) AND ((surgical wound infection) OR (surgical wound dehiscence) OR (wound healing) OR ('wound complication')).

Eligibility

We applied the following inclusion criteria: a minimum patient age of 18 years was set to enable comparisons between fully grown adults only; only publications written in German or English were included. Our exclusion criteria were an overall modified Coleman Methodology Score (mCMS) <60, follow-up rate <80%, traumatic amputations, and animal studies.

The same reviewers independently screened titles and abstracts for relevance according to the aforementioned inclusion and exclusion criteria. If no abstract was available, the full text was obtained to assess the study's relevance. To make sure not to overlook any suitable studies, we cross-referenced the references within included articles if they had been missed by our search algorithm. Appropriate publications were then independently analyzed for the mCMS and level of evidence according to the Oxford Centre of Evidence-Based Medicine (10).

Outcome criteria

Patient demographics, number of patients, type of iNPWT procedure, post-surgical 30-day mortality, readmission, and wound complication rate were extracted (Table 1).

Statistical analysis

To analyze the collected data, RevMan 5® was used. Comparative analyses of post-surgical wound complications, readmission rate, and of 30-day mortality were performed and the odds ratios were calculated. Those results were then visualized in forest plots.

Results

Study selection

Our literature search and study selection procedure are depicted in Fig. 1, and a total of 484 papers were identified by our search algorithm. Moreover, three papers were added from the reference list. These papers were scanned, and any duplicates or topic-unrelated articles were excluded. After analyzing the eligibility criteria, three of the seven studies could be included in our quantitative analysis (2, 11, 12). There were three retrospective case–control studies containing a total of 457 patients.

The number of patients included in the selected studies ranged from 54 to 309 with a mean age of 66.6 ± 5.6 years for iNPWT group and 66.7 ± 8.3 years for the control group.

Risk of bias assessment

All included studies possessed an evidence-level III. There is a high risk of selection bias considering the retrospective design of the included studies. Reporting and detection biases are considerable due to the lack of randomization and blinding.

Our results for the risk of bias assessment are shown in Fig. 2.

Postoperative infection and rate of 30-day mortality

Overall complications, including readmissions, revision surgery as well as surgical-site infection, were assessed

Table 1 Study demographics.

Study	Patients, *n*	Age (years)	Sex (M:F)	Type of iNPWT	Wound complications	Revision surgery	Readmission	30-day-mortality
Chang *et al.* (21)	54		31:23					
iNPWT	23	67 ± 12	14:9	Prevena†	3	1	1	1***
SWC	31	73 ± 15	17:14		12	3	3	1***
Gantz *et al.* (11)	94*		3645/1592**	ND		ND		
iNPWT	47	59.65**			1		6	1
SWC	47	54.92**			4		7	3
Stenqvist *et al.* (2)	309		192:117		ND		ND	
iNPWT	139	73.3	87:52	Prevena†		17		22
SWC	170	71.8	105:65			27		30

*Matched controls in subgroup – total: 5237, closed incisions: 3320; **Not specified in subgroup; ***Perioperative mortality; †specialized NPWT system by KCI, Acelity.
M:F, male:female; ND, not defined;SWC, standard wound care.

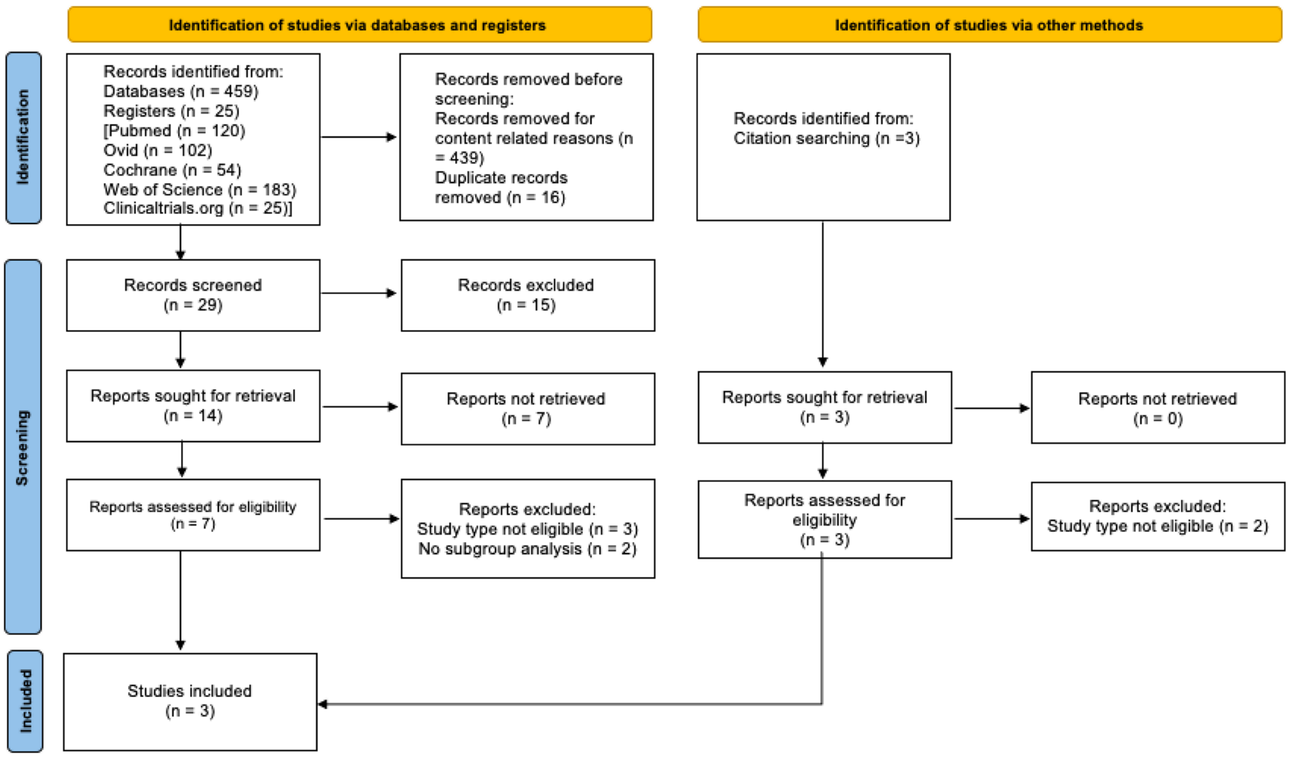

Figure 1
PRISMA flow chart.

in all three studies containing a total of 457 patients. As we found low heterogeneity (I^2 = 0%; P=0.18), a random-effects model was used for further subgroup analysis. Overall, the risk for post-surgery complications was significantly reduced when iNPWT was applied (OR=0.52; 95% CI: 0.30–0.89; P=0.02). Subgroup analysis revealed a significantly lower wound infection rate when iNPWT was used for wound dressing (OR= 0.24; 95% CI: .07–.78; P=0.02). A meta-analysis based on these data is shown in Figs 4 and 5, respectively.

We also conducted a meta-analysis to calculate potential differences in the rate of readmissions and revision surgeries. However, there was no significant improvement in rate of readmission and surgical revision. Detailed results are depicted in Figs 5 and 6.

Data on 403 patients revealed an overall number of 56 cases of 30-day mortality after major limb amputation. 30-day mortality rates were 12.4% for iNPWT and 15.2% with standard wound dressing. We identified a difference in the rate of 30-day mortality in conjunction with the type of wound dressing used (OR=0.48; 95% CI: 0.46–1.45; P=0.48) (Fig. 3). However, there was no statistical significance.

Discussion

Lower extremity amputation is associated with a high risk of wound complications and mortality (2, 13, 14). In high-risk surgical wounds, iNPWT showed to have promising clinical effects in lowering post-surgery infection rates.

Study	Pre-Intervention		At Intervention	Post-Intervention				Overall risk of bias
	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of the outcome	Bias in selection of the reported result	
Chang 2020	serious	low	low	NI	NI	NI	NI	serious
Gantz 2020	moderate	moderate	NI	NI	low	moderate	NI	moderate
Stenqvist 2019	serious	low	low	low	low	low	NI	serious

Key:	low risk of bias	moderate risk	serious risk	critical risk	NI - no information

Figure 2
Risk of bias assessment via ROBINS-1.

Study or Subgroup	iNPWT Events	iNPWT Total	standard wound care Events	standard wound care Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Gantz 2020	1	47	3	47	11.4%	0.32 [0.03, 3.18]
Stenqvist 2019	22	139	30	170	88.6%	0.88 [0.48, 1.60]
Total (95% CI)		**186**		**217**	**100.0%**	**0.81 [0.46, 1.45]**
Total events	23		33			
Heterogeneity: Chi² = 0.70, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.48)						

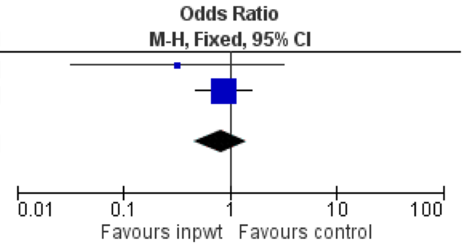

Figure 3
Meta-analysis of 30-day mortality.

Summarizing the outcomes of this meta-analysis, our study's key finding is that post-surgical complications, in particular surgical-site infections, are significantly less likely to occur when the patient in question has undergone incisional negative wound therapy. However, this kind of wound dressing does not seem to influence the rate of 30-day mortality significantly.

In standard gauze wound dressings, dressings have to be changed in a repetitive interval. Depending on the postinterventional bleeding from the wound, repetitive changes are necessary within the first 5 days after surgery (11, 15, 16). Thus, not only does the microenvironment of the wound gets disrupted but a change of dressing is done at the bedside under semi-sterile circumstances, which leads to a higher risk of surgical-site infection (1, 17). iNPWT is applied directly after surgery, which guarantees for more sterility and does not need a change of dressings mostly within the first 4–5 days after surgery (18).

On a cellular level, negative pressure promotes the removal of the excessive interstitial fluid and inflammatory mediators within subcutaneous tissue and also stimulates cell proliferation and microperfusion due to focal pressure stimuli (19, 20, 21, 22). Activation, migration, and proliferation of fibroblasts are already detectable within the first 48 h after application (23). Furthermore, iNPWT has a mechanical effect, because both wound edges are pressed against each other and thus lowering the risk of wound dehiscence (20).

This is especially of interest in patients with hindered microcirculation, to optimize dermal healing at surgical sites (3).

As reported by Zayan *et al.* and Semsarzadeh *et al.*, and also seen in our investigations, iNPWT was associated with a significantly lower prevalence of wound infections. This leads ultimately to an accelerated time of rehabilitation, prosthetic fitting, and improvement of life quality (18, 24).

Wound healing is a prerequisite for rehabilitation; however, survival is influenced by many factors. Usually, diabetes or peripheral occlusive disease also impairs vital organ functions which possibly leads to the missing effect on 30-day mortality. Patients undergoing amputation represent cases of end-stage diabetes or peripheral artery disease (PAD), where all options for limb salvage are exhausted. Referring to diabetes, end-stage comorbidities include diabetic nephropathy (DKD) as well as diabetic cardiomyopathy. In patients with DKD, the mortality rate is 30 times higher (25). In a meta-analysis concerning long-term mortality in lower limb amputations, Stern *et al.* calculated a two-fold higher mortality rate, when cardiac or renal comorbidities were present (26).

Healing processes in multi-morbid patients are complex and are influenced by many factors. There are certain intrinsic risk factors that make one patient more prone to wound complications than another (5, 27, 28). The use of tobacco, for example, slows healing, as nicotine impairs cell proliferation and causes vasoconstriction (29, 30, 31). There are additional cofactors influencing healing and thus increase the likelihood of wound infections (diabetes, obesity, corticosteroids, and high-tension wounds). In an international expert panel, it was stated that with the presence of any of those risk factors, iNPWT should be considered as a wound dressing (5). Patients undergoing

Study or Subgroup	inpwt Events	inpwt Total	standard wound dressing Events	standard wound dressing Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Chang 2020	3	23	12	31	23.5%	0.24 [0.06, 0.98]
Gantz 2020	2	47	8	47	20.2%	0.22 [0.04, 1.08]
Stenqvist 2019	17	139	27	170	56.3%	0.74 [0.38, 1.42]
Total (95% CI)		**209**		**248**	**100.0%**	**0.52 [0.30, 0.89]**
Total events	22		47			
Heterogeneity: Chi² = 3.43, df = 2 (P = 0.18); I² = 42%						
Test for overall effect: Z = 2.39 (P = 0.02)						

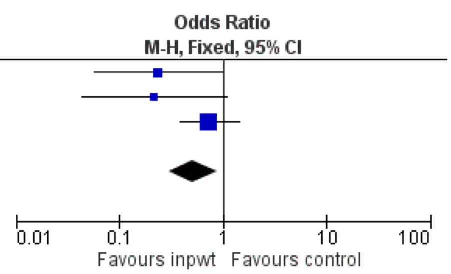

Figure 4
Meta-analysis of postoperative complications.

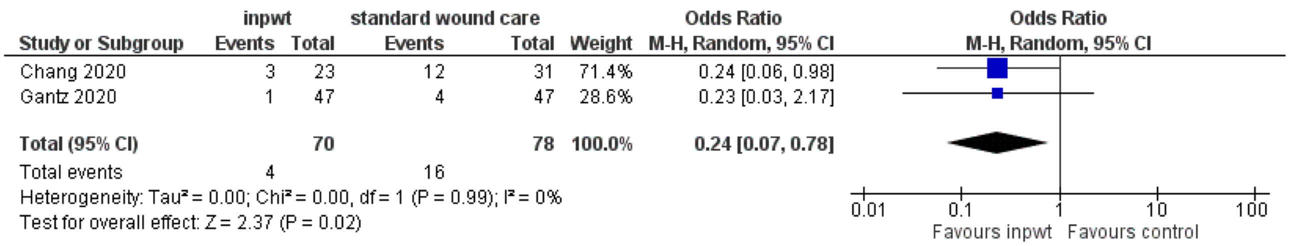

Figure 5
Meta-analysis of postoperative wound complications.

major limb amputation often present with at least one of these risk factors. Thus, iNPWT should be considered for routine utilization to decrease the risk of wound infections.

Limitations

There are limitations to this study inherent in the type of publications we included and in our search algorithm. Our search strategy followed an English search algorithm. Potentially suitable publications in other languages were not considered. The risk of publication bias is imminent because only published articles were included. To minimize this kind of bias, the CochraneLibrary® was scanned for clinical trials, but we detected no relevant findings, as the results of several ongoing trials have not been published yet.

All of the publications we included are retrospective case–control studies entailing a high risk for selection, detection, and reporting bias. To exclude methodologically inadequate studies, we focused on bias assessment as done by ROBINS-I and mCMS. There was no critical risk of bias in any included study. As 'Prevena®' is a specially designed NPWT system by KCI Medizinprodukte GmbH and was exclusively used in the studies of Stenquvist *et al.* and Chang *et al.*, funding bias seems to be possible. However, there was no information about sponsoring or funds received from KCI.

Conclusion

Overall, the usage of iNPWT may reduce the risk of postoperative wound complications in major lower limb amputations but does not improve 30-day mortality rates significantly. However, to anticipate surgical-site infection, especially in multi-morbid patients, iNPWT has shown effectiveness and thus should be used whenever applicable.

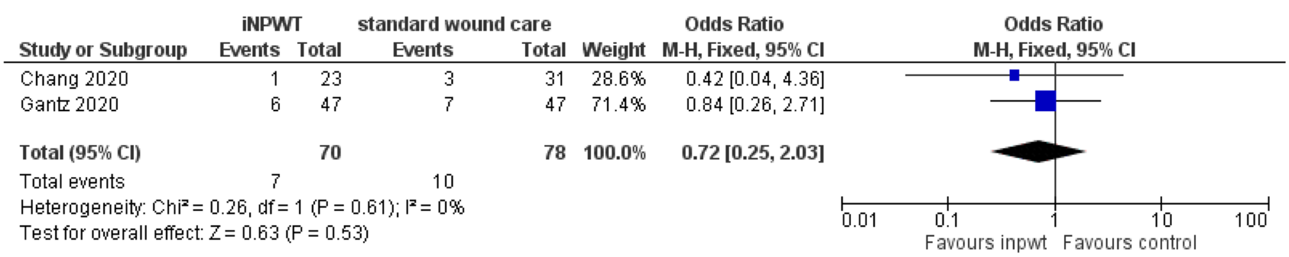

Figure 6
Meta-analysis of readmission rate.

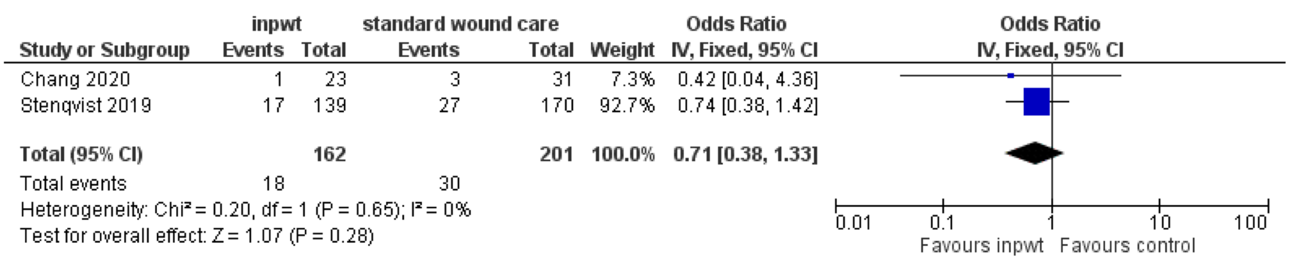

Figure 7
Meta-analysis of revision surgery.

ICMJE Conflict of Interest Statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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