1 Bijlage Evidence tabellen en GRADE profielen

Onderzoeksvraag 1

Wat is het effect van antibiotica, verbandmaterialen en wondreiniging op geuroverlast bij patiënten met een oncologische ulcus in de palliatieve fase?

Onderzoeksvraag

P	Patiënten (≥ 18 jaar) met geuroverlast door oncologische ulcera in de palliatieve fase
I	Antibiotica, verbandmaterialen, wondreiniging
C	Andere interventie, geen interventie, placebo
O	Geur, kwaliteit van leven

Systematische reviews: Evidence tabel

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Adderley 2014	Design: systematic review Funding: National Institue for health Research; CoI: none Search date: Aug 2013 Databases: Cochrane Wounds Group Specialised Register, Central, Medline, Embase, Cinahl Study designs: RCT's, CCTs N included studies: N=4	Eligibility criteria: people of any age, male and female, in any care setting, who had been clinically diagnosed with fungating wounds due to any type of carcinoma	Topical agents and dressings, or dressing systems, applied to fungating wounds	CRITICAL OUTCOMES Odour: Bower 1992: VAS 0-10, graded daily by patient and 1 investigator; in the placebo group (N=5), the mean patient and medical staff odour assessment remained above 6/10 (the minimum severity required for inclusion in the study); in the metronidazole group (N=4) the mean patient odour assessment fell from 7.8 on day 0, to 5.0 on day 6 (p>0.1), and the mean medical staff odour assessment fell from 6.5 on day 0, to 4.3 on day 6 (p>0.1); no statistically significant difference between the two groups Kalemikerakis 2012: categorical, graded weekly for 4 weeks by health professionals; in the final assessment (week 4), in the group who received foam with silver, a decrease of malodour was reported in 10 patients (76.9%) while in 3 patients (23.1%)	Review process by two independent reviewers No search restrictions Relevant included studies: Bower 1992, Kalemikerakis 2012, Lund-Nielsen 2011

				malodour stayed the same; odour did not increase in any patients; in the group who received the foam dressings without silver, decrease of malodour was reported in 4 patients (30.8%) while in 9 (69.2%) malodour stayed the same; odour did not increase in any patients; the difference in odour reduction between the two groups was statistically significant (p=0.049) Lund-Nielsen 2011: VRS and VAS; no statistically significant difference was found between the patients treated with honey-coated dressings and those treated with silver-coated dressings Quality of life: not reported	
da Costa Santos 2010	Design: systematic review Funding: not reported; CoI: not reported Search date: Aug 2006 Databases: Thesis Bank, Capes and Digital Library of Theses and Dissertations, Proquest Dissertation and Theses, Current Controlled Trials, BDENF, CINAHL, Embase, PubMed, Ovid, PsycInfo, Scopus, and Web of Science, Lilacs, EBM Reviews Study designs: all N included studies: N=20	Eligibility criteria: individuals with malignant neoplasms who developed malignant fungating wounds	Topical treatments	No separate results reported for Bower 1992 and Upright 1994	Unclear if review process was done by independent reviewers Unclear if restrictions were used Relevant included studies: Bower 1992, Upright 1994
Finlayson 2017	Design: systematic review Funding: not reported; CoI: none Search date: Sep 2015 Databases: Medline, Embase, Cochrane Library, Cinahl Study designs: RCT's, pre/post studies	Eligibility criteria: participants who were diagnosed with cancer and a malignant wound (fungating, infiltrative, ulcerating) not related to surgery or radiation therapy Exclusion: systematic reviews, clinical guidelines, case series, and case reports	Topical analgesics with or without additional inert substances for the management of pain and/or topical antimicrobials with or without additional odour-reducing topical agents for the prevention or	CRITICAL OUTCOMES Odour: Bower 1992: no significant difference in odour between groups Lian 2014: no significant difference in odour between groups Lund-Nielsen 2011: no significant difference in malodour between groups	Review process by two independent reviewers Restricted to English Relevant included studies: Bower 1992, Lian 2014, Lund-Nielsen 2011, Upright 1994

	N included studies: N=5		management of infection and infection-related odours	Upright 1994: significant increase in odour control in the intervention group compared with the control group Quality of life: not reported	
Gethin 2023	Design: systematic review Funding: Science Foundation Ireland (SFI) and B. Braun Hospicare Ltd., European Regional Development Fund under Grant Number 13/RC/2073; CoI: none Search date: unclear Databases: EMBASE, Ovid MEDLINE, CINAHL, CENTRAL, PubMed, Web of Science and Scopus Study designs: RCT's N included studies: N=5	Eligibility criteria: adults (18 years and over) with chronic wounds including venous, arterial, mixed arterial venous, diabetic or pressure ulcers or those with malignant fungating wounds Exclusion: people solely with burns, acute wounds, surgical wounds, or atypical wounds	Topical interventions	CRITICAL OUTCOMES Odour: Bower 1992: mean patient and medical-staff odour assessment in the placebo group remained above 6; in contrast, in the treatment group, the mean patient odour assessment fell from 7.8 on day zero to 5.0 on day six and odour as graded by medical staff fell from a mean of 6.5 to 4.3 on day six; both findings were non-significant Kalemikerakis 2012: difference in odour reduction (yes/no) between the two groups was borderline statistically significant (p=0.049) Lian 2014: no significant difference in the improvement of odour between the groups Villela-Castro 2018: no significant differences in odour between metronidazole and polyhexanide gel at any stage of the study Quality of life: Lian 2014: self-developed five-point questionnaire; no statistical significant improvement when compared between the two groups Villela-Castro 2018: Ferrans and Powers Quality of Life Index – Wounds Version; no significant differences between individuals who received treatment of topical metronidazole compared to polyhexanide gel	Review process by two independent reviewers Unclear if search restrictions were used Relevant included studies: Bower 1992, Kalemikerakis 2012, Lian 2014, Villela-Castro 2018
Ramasubbu 2017	Design: systematic review Funding: National Institute for Health Research; CoI: none Search date: Mar 2017 Databases: Cochrane Wounds Specialised Register, CENTRAL, Medline, Embase, Cinahl	Eligibility criteria: people of any age with a clinically diagnosed malignant wound resulting from any type of cancer	Any systemic antibiotic used in the treatment of any type of malignant wound	CRITICAL OUTCOMES Odour: mean smell score (0-3), MD -2.16, 95%CI -3.6 to -0.72 Quality of life: not reported	Review process by two independent reviewers No search restrictions Relevant included studies: Ashford 1984

	Study designs: RCT's N included studies: N=1				
Wiese 2023	Design: systematic review Funding: not reported; CoI: none Search date: June 2018 Databases: PubMed, Cinahl, Embase, CENTRAL, PsycInfo Study designs: RCT's N included studies: N=7	Eligibility criteria: cancer patients and former cancer patients Exclusion: patients with precancerous lesions or carcinoma in situ; primary prevention; preclinical studies	Green tea and green tea extract	CRITICAL OUTCOMES Odour: Lian 2014: no significant difference in the improvement of odour between the groups Quality of life: Lian 2014: self-developed five-point questionnaire; no statistical significant improvement when compared between the two groups, except for interference of odour with social activities (p=0.04)	Review process by two independent reviewers Restricted to English and German Relevant included studies: Lian 2014

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; MD: mean difference; RCT: randomised controlled trial.

References

Adderley UJ, Holt IG. Topical agents and dressings for fungating wounds. Cochrane Database Syst Rev. 2014(5):CD003948.

Ashford R, Plant G, Maher J, Teare L. Double-blind trial of metronidazole in malodorous ulcerating tumours. Lancet. 1984;1(8388):1232-3.

Bower M, Stein R, Evans TRJ, Hedley A, Pert P, Coombes RC. A double-blind study of the efficacy of metronidazole gel in the treatment of malodorous fungating tumours. European Journal of Cancer Part A: General Topics. 1992;28(4-5):888-9.

da Costa Santos CM, de Mattos Pimenta CA, Nobre MR. A systematic review of topical treatments to control the odor of malignant fungating wounds. J Pain Symptom Manage. 2010;39(6):1065-76.

Finlayson K, Teleni L, McCarthy AL. Topical Opioids and Antimicrobials for the Management of Pain, Infection, and Infection-Related Odors in Malignant Wounds: A Systematic Review. Oncol Nurs Forum. 2017;44(5):626-32.

Gethin G, Vellinga A, McIntosh C, Sezgin D, Probst S, Murphy L, et al. Systematic review of topical interventions for the management of odour in patients with chronic or malignant fungating wounds. J Tissue Viability. 2023;32(1):151-7.

Kalemikerakis J, Vardaki Z, Fouka G, Vlachou E, Gkovina U, Kosma E, et al. Comparison of foam dressings with silver versus foam dressings without silver in the care of malodorous malignant fungating wounds. J. 2012;17(3):560-4.

Lian SB, Xu Y, Goh SL, Aw FC. Comparing the effectiveness of green tea versus topical metronidazole powder in malodorous control of fungating malignant wounds in a controlled randomised study. Proceedings of Singapore Healthcare. 2014;23(1):3-12.

Lund-Nielsen B, Adamsen L, Kolmos HJ, Rorth M, Tolver A, Gottrup F. The effect of honey-coated bandages compared with silver-coated bandages on treatment of malignant wounds - a randomized study. Wound Repair and Regeneration 2011;19(6):664-70.

Ramasubbu DA, Smith V, Hayden F, Cronin P. Systemic antibiotics for treating malignant wounds. Cochrane Database Syst Rev. 2017;8:CD011609.

Upright CA, Salton C, Roberts F, Murphy J. Evaluation of Mesalt dressings and continuous wet saline dressings in ulcerating metastatic skin lesions. Cancer Nurs. 1994;17(2):149-55.

Villela-Castro DL, Santos V, Woo K. Polyhexanide Versus Metronidazole for Odor Management in Malignant (Fungating) Wounds: A Double-Blinded, Randomized, Clinical Trial. J Wound Ostomy Continence Nurs. 2018;45(5):413-8.

Wiese F, Kutschan S, Doerfler J, Mathies V, Buentzel J, Buentzel J, et al. Green tea and green tea extract in oncological treatment: A systematic review. Int J Vitam Nutr Res. 2023;93(1):72-84.

GRADE tabellen – Geïncludeerde studies

Reference: Kalemikerakis J, Vardaki Z, Fouka G, Vlachou E, Gkovina U, Kosma E, et al. Comparison of foam dressings with silver versus foam dressings without silver in the care of malodorous malignant fungating wounds. J. 2012;17(3):560-4.

Question: Foam dressing containing silver compared to foam dressing without silver in patients with malodorous fungating malignant wounds

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**foam dressing containing silver**	**foam dressing without silver**	**Relative (95% CI)**	**Absolute (95% CI)**		
Odour (categorical)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	10/13 (76.9%)	4/13 (30.8%)	**RR 2.50** (1.05 to 5.96)	**462 more per 1.000** (from 15 more to 1.000 more)	⨁⨁◯◯ Low	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Kalemikerakis 2012: unclear randomisation method, allocation concealment and blinding

b. CI around RR includes 1.25

Author(s): Lian SB, Xu Y, Goh SL, Aw FC. Comparing the effectiveness of green tea versus topical metronidazole powder in malodorous control of fungating malignant wounds in a controlled randomised study. Proceedings of Singapore Healthcare. 2014;23(1):3-12.

Question: Green tea dressing compared to metronidazole powder in cancer patients with malodorous fungating wounds

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**green tea dressing**	**metronidazole powder**	**Relative (95% CI)**	**Absolute (95% CI)**		
Malodorous score rated by patients using VNS (0 to 10) on day 7												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Median [min-max]: 1 [0-4] vs. 0 [0-4], p=0.29				⊕⊕◯◯ Low	CRITICAL
Malodorous score rated by assigned nurses using VNS (0 to 10) on day 7												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	Median [min-max]: 1 [0-4] vs. 0 [0-4], p=0.12				⊕⊕◯◯ Low	CRITICAL
Interference of malodour with life over last week												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	Day 1: mean rank 17.17 vs. 13.83, p=0.30 Day 7: mean rank 16.27 vs. 14.73, p=0.59				⊕⊕◯◯ Low	CRITICAL
Interference of malodour with level of physical comfort over last week												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	Day 1: mean rank 17.17 vs. 13.83, p=0.30 Day 7: mean rank 16.70 vs. 14.30, p=0.41				⊕⊕◯◯ Low	CRITICAL
Interference of malodour with appetite over last week												

1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	Day 1: mean rank 15.27 vs. 15.73, p=0.88 Day 7: mean rank 17.27 vs. 13.73, p=0.22	⊕⊕◯◯ Low	CRITICAL
Interference of malodour with social activities over last week									
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	Day 1: mean rank 18.73 vs. 12.27, p=0.04 Day 7: mean rank 17.13 vs. 13.87 p=0.28	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval

Explanations

a. Lian 2014: no blinding

b. CI around estimated SMD includes 0.5

c. Small sample size

Author(s): Lund-Nielsen B, Adamsen L, Kolmos HJ, Rorth M, Tolver A, Gottrup F. The effect of honey-coated bandages compared with silver-coated bandages on treatment of malignant wounds - a randomized study. Wound Repair and Regeneration 2011;19(6):664-70.

Question: Manuka honey-coated dressings compared to silver-coated dressings in patients with advanced stage cancer and malignant wounds

Setting:

Bibliography:

Certainty assessment							**№ of patients**		**Effect**		**Certainty**	**Importance**
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**manuka honey-coated dressings**	**silver-coated dressings**	**Relative (95% CI)**	**Absolute (95% CI)**		
Malodour												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	VRS: no significant difference between groups, p=0.862				⊕◯◯◯ Very low	CRITICAL

							VAS 0-10: no significant difference between groups, p= 0.551					
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval

Explanations

a. Lund-Nielsen 2011: unclear allocation concealment and blinding

b. No quantification of precision possible

Author(s): Upright CA, Salton C, Roberts F, Murphy J. Evaluation of Mesalt dressings and continuous wet saline dressings in ulcerating metastatic skin lesions. Cancer Nurs. 1994;17(2):149-55.

Question: Mesalt dressings compared to continuous wet saline dressings in patients with ulcerating metastatic skin lesions

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Mesalt dressings**	**continuous wet saline dressings**	**Relative (95% CI)**	**Absolute (95% CI)**		
Control of odor (VAS, 10 cm)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	7.48 vs. 3.69 cm, p<0.05				⨁◯◯◯ Very low	CRITICAL
Quality of life - not reported												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval

Explanations

a. Upright 1994: unclear randomisation method and allocation concealment, no ITT analysis

b. Very small sample size, OIS not reached

Author(s): Bower M, Stein R, Evans TRJ, Hedley A, Pert P, Coombes RC. A double-blind study of the efficacy of metronidazole gel in the treatment of malodorous fungating tumours. European Journal of Cancer Part A: General Topics. 1992;28(4-5):888-9.

Question: Metronidazole gel compared to placebo in patients with malodorous open fungating primary or metastatic tumours

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**metronidazole gel**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Odour (VAS 0-10)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	Mean patient and medical-staff odour assessment in the placebo group remained above 6; in contrast, in the treatment group, the mean patient odour assessment fell from 7.8 on day zero to 5.0 on day six and odour as graded by medical staff fell from a mean of 6.5 to 4.3 on day six; both findings were non-significant				⨁◯◯◯ Very low	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval

Explanations

a. Bower 1992: unclear randomisation method, allocation concealment and blinding

b. Very small sample size

Author(s): Ashford R, Plant G, Maher J, Teare L. Double-blind trial of metronidazole in malodorous ulcerating tumours. Lancet. 1984;1(8388):1232-3.

Question: Systemic metronidazole compared to placebo in patients with malignant wounds

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**systemic metronidazole**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Malodour: mean smell score												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	6	6	-	MD **2.16 lower** (3.6 lower to 0.72 lower)	⨁◯◯◯ Very low	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Ashford 1984: unclear randomisation method and allocation concealment, no ITT analysis

b. Very small sample size (6 participants)

Author(s): Villela-Castro DL, Santos V, Woo K. Polyhexanide Versus Metronidazole for Odor Management in Malignant (Fungating) Wounds: A Double-Blinded, Randomized, Clinical Trial. J Wound Ostomy Continence Nurs. 2018;45(5):413-8.

Question: Topical metronidazole 0.8% solution compared to topical polyhexanide 0.1% solution in patients with malignant (fungating) wounds

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**topical metronidazole 0.8% solution**	**topical polyhexanide 0.1% solution**	**Relative (95% CI)**	**Absolute (95% CI)**		
Odour quality, rated by patient on day 4												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	12	12	-	MD **0.41 lower** (1.1 lower to 0.28 higher)	⨁⨁◯◯ Low	CRITICAL
Odour impact, rated by patient on day 4												
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	12	12	-	MD **0.41 higher** (0.68 lower to 1.5 higher)	⨁◯◯◯ Very low	CRITICAL
Ferrans and Powers Quality of Life Index												

1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	12	12	-	MD **0.01 higher** (1.38 lower to 1.4 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; **MD:** mean difference

Explanations

a. Villela-Castro 2018: unclear allocation concealment and ITT analysis

b. CI around estimated SMD includes -0.50

c. CI around estimated SMD includes -0.50 and 0.50

Onderzoeksvraag 2

Wat is het effect van verbandmateriaal, radiotherapie, tranexaminezuur, xylometazoline, adrenaline, embolisatie, elektrocoagulatie, of zilvernitraat op bloedverlies bij patiënten met een oncologische ulcus in de palliatieve fase?

Onderzoeksvraag

P	Patiënten (≥ 18 jaar) met acute of chronische bloeding bij oncologische ulcera in de palliatieve fase
I	Verbandmateriaal, radiotherapie, tranexaminezuur, xylometazoline, adrenaline, embolisatie, elektrocoagulatie, zilvernitraat
C	Andere interventie, geen interventie, placebo
O	Bloedverlies, kwaliteit van leven

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Adderley 2014	Design: systematic review Funding: National Institue for health Research; CoI: none Search date: Aug 2013 Databases: Cochrane Wounds Group Specialised Register, Central, Medline, Embase, Cinahl Study designs: RCT's, CCTs N included studies: N=4	Eligibility criteria: people of any age, male and female, in any care setting, who had been clinically diagnosed with fungating wounds due to any type of carcinoma	Topical agents and dressings, or dressing systems, applied to fungating wounds	No relevant studies identified	Review process by two independent reviewers No search restrictions Relevant included studies: none
Firmino 2021	Design: systematic review Funding: University of Sao Paulo - School of Nursing, Sao Paulo, Brazil; CoI: none Search date: Apr 2020 Databases: PubMed, Cochrane, Embase, Scopus, Web of Science, CINAHL, Virtual Library of Salud portal Study designs: all N included studies: N=6	Eligibility criteria: primary studies that investigated treatments, interventions, or any topical measures for the control of bleeding from breast malignant fungating wounds in adults Exclusion: local measures such as surgery, radiotherapy, chemoembolization, and electrochemotherapy	Topical treatment	No relevant studies identified	Review process by two independent reviewers Restricted to Portuguese, English and Spanish literature Relevant included studies: none

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Firmino 2023	Design: RCT Funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (award no. 001), School of Nursing of the University of São Paulo (Escola de Enfermagem da Universidade de São Paulo) and the National Cancer Institute/Ministry of Health (Instituto Nacional de Câncer/Ministério da Saúde) of Brazil; CoI: none Setting: 2 hospitals of the National Cancer Institute (Instituto Nacional do Cancer [INCA]) in Brazil Sample size: N=28 Duration: recruitment Oct 2017 – Aug 2018	Eligibility criteria: patients older than 18 years, with a malignant breast cancer wound at any stage, with bleeding, who accepted venipuncture for blood collection Exclusion criteria: patients with bleeding that seemingly came from arterial hemorrhages, patients with bleeding that made it impossible to identify its exact origin (affecting the process of application and evaluation of results of planned hemostatic interventions), patients with topical hemostatics that adhered to the wound bed, unconscious patients, patients with no family members present, patients with associated hematologic diseases, patients who were consciously allergic to the topical products used in the study, and patients who participated in the study, in previous episodes of bleeding *A priori* patient characteristics: M/F: 0/28 Mean age: 57.7y	Calcium alginate (N=13) vs. Oxidized regenerated cellulose (N=15)	CRITICAL OUTCOMES Blood loss: Total time for hemostasis: mean (or median?), 30.4 sec (95%CI 21.7-) vs. 30.1 sec (95%CI 18.6-189), p=0.894 Proportion of patients achieving hemostasis: 30 sec: 46.1% vs. 50% 3 min: 92.2% vs. 85.7% 5 min: 92.2% vs. 85.7% 10 min: 100% vs. 92.8% Proportion of patients requiring >1 unit of hemostatic product due to bleeding recurrence: 15.3% vs. 33.3% Mean number of units of hemostatic product consumed: 1.2 vs. 2.6 units Quality of life: not reported	Level of evidence: high risk of bias Randomization was prepared by a statistician using envelopes to be raffled; each envelope was sequentially numbered and identified by bleeding intensity, generating 3 blocks (strata) of patient allocation (mild, moderate, and severe bleeding) The assistant researcher generated a randomized allocation sequence and assigned interventions to the study participants Open label study Unclear ITT analysis Several data seem to be reported incorrectly

Abbreviations: 95%CI: 95% confidence interval; CCT: controlled clinical trial; CoI: conflict of interest; ITT: intention to treat; RCT: randomised controlled trial.

References

Adderley UJ, Holt IGS. Topical agents and dressings for fungating wounds. Cochrane Database Syst Rev. 2014;2014(5).

Firmino F, Villela-Castro D, Santos V. Oxidized Regenerated Cellulose Versus Calcium Alginate in Controlling Bleeding From Malignant Wounds: A Randomized Controlled Trial. Cancer Nurs. 2023;13:13.

Firmino F, Villela-Castro DL, Santos JD, Conceicao de Gouveia Santos VL. Topical Management of Bleeding From Malignant Wounds Caused by Breast Cancer: A Systematic Review. J Pain Symptom Manage. 2021;61(6):1278-86.

GRADE tabellen – Geïncludeerde studies

Author(s): Firmino F, Villela-Castro D, Santos V. Oxidized Regenerated Cellulose Versus Calcium Alginate in Controlling Bleeding From Malignant Wounds: A Randomized Controlled Trial. Cancer Nurs. 2023;13:13.

Question: Calcium alginate compared to oxidised regenerated cellulose in patients with a malignant breast cancer wound

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**calcium alginate**	**oxidised regenerated cellulose**	**Relative (95% CI)**	**Absolute (95% CI)**		
Total time for hemostasis												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	Mean (or median?): 30.4 sec (95%CI 21.7-) vs. 30.1 sec (95%CI 18.6-189), p=0.894				⨁◯◯◯ Very low	CRITICAL
Proportion of patients achieving hemostasis at 30 sec												
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	Calcium alginate: N=3, 46.1% Oxidized regenerated cellulose: N=7, 50%				⨁◯◯◯ Very low	CRITICAL
Proportion of patients achieving hemostasis at 3 min												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	12/13 (92.3%)	12/14 (85.7%)	**RR 1.08** (0.83 to 1.40)	**69 more per 1.000** (from 146 fewer to 343 more)	⨁⨁◯◯ Low	CRITICAL
Proportion of patients achieving hemostasis at 5 min												

1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	12/13 (92.3%)	12/14 (85.7%)	**RR 1.08** (0.83 to 1.40)	**69 more per 1.000** (from 146 fewer to 343 more)	⊕⊕◯◯ Low	CRITICAL
Proportion of patients achieving hemostasis at 10 min												
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	13/13 (100.0%)	13/14 (92.9%)	**RR 1.07** (0.88 to 1.30)	**65 more per 1.000** (from 111 fewer to 279 more)	⊕⊕◯◯ Low	CRITICAL
Proportion of patients requiring >1 unit of hemostatic product due to bleeding recurrence												
1	randomised trials	serious[a]	not serious	not serious	very serious[e]	none	2/13 (15.4%)	5/15 (33.3%)	**RR 0.46** (0.11 to 1.99)	**180 fewer per 1.000** (from 297 fewer to 330 more)	⊕◯◯◯ Very low	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Firmino 2023: open label study

b. Optimal information size not reached; unclear from article if the reported data are means or medians

c. Reported numbers and proportions do not match total number of patients

d. CI around RR includes 1.25

e. CI around RR includes 0.75 and 1.25

Onderzoeksvraag 3

Om de uitgangsvraag van deze module te kunnen beantwoorden, is een systematisch literatuuronderzoek uitgevoerd. De onderzoeksvraag die hiervoor is opgesteld is PICO-gestructureerd en luidt: Wat is het effect van systemische en lokale pijnstilling, radiotherapie en verbandmateriaal op pijn bij patiënten met een oncologische ulcus in de palliatieve fase?

Onderzoeksvraag

P	Patiënten (≥ 18 jaar) met pijn bij oncologische ulcera in de palliatieve fase
I	Systemisch en lokale pijnstilling, radiotherapie, verbandmateriaal
C	Andere interventie, geen interventie, placebo
O	Pijn, kwaliteit van leven

Systematische reviews

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Adderley 2014	Design: systematic review Funding: National Institue for health Research; CoI: none Search date: Aug 2013 Databases: Cochrane Wounds Group Specialised Register, Central, Medline, Embase, Cinahl Study designs: RCT's, CCTs N included studies: N=4	Eligibility criteria: people of any age, male and female, in any care setting, who had been clinically diagnosed with fungating wounds due to any type of carcinoma	Topical agents and dressings, or dressing systems, applied to fungating wounds	CRITICAL OUTCOMES Pain: "No statistically significant difference was found between the patients treated with honey-coated dressings and those treated with silver-coated dressings" Quality of life: not reported	Review process by two independent reviewers No search restrictions Relevant included studies: Lund-Nielsen 2011
Finlayson 2017	Design: systematic review Funding: not reported; CoI: none Search date: Sep 2015 Databases: Medline, Embase, Cochrane Library, Cinahl Study designs: RCT's, pre/post studies N included studies: N=5	Eligibility criteria: participants who were diagnosed with cancer and a malignant wound (fungating, infiltrative, ulcerating) not related to surgery or radiation therapy Exclusion: systematic reviews, clinical guidelines, case series, and case reports	Topical analgesics with or without additional inert substances for the management of pain and/or topical antimicrobials with or without additional odour-reducing topical agents for the prevention or management of infection and infection-related odours	CRITICAL OUTCOMES Pain: no significant differences between groups at baseline or after the four-week intervention for any outcome Quality of life: not reported	Review process by two independent reviewers Restricted to English Relevant included studies: Lund-Nielsen 2011

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Ciałkowska-Rysz 2019	Design: cross-over RCT Funding: none; CoI: none Setting: single university centre, Poland Sample size: N=35 Duration: 14 days	Eligibility criteria: adult patients with localized cancer-related pain and treated with systemic opioids Exclusion criteria: chemotherapy or radiotherapy in the past 1 month before the study; local skin or mucosa infection; local irritation or other side effects related to application of the gel *A priori* patient characteristics: M/F: 13/22 Mean age: 61.6y	Topical morphine 0.2% gel on mucosal lesions or 0.2% ointment on skin lesions (without restrictions regarding the number of doses per day) (N=35) vs. Placebo (N=35)	CRITICAL OUTCOMES Pain: Mean pain intensity (NRS 0-10): Day 7: 2.5 (95%CI 1.6-3.3) vs. 4.6 (3.3-5.9), p<0.0001 Day 14: 2.5 (1.6-3.4) vs. 5.2 (4.4-6.1), p<0.0001 Pain relief (% change from baseline in pain intensity): 57% vs. 16%, p=0.0000004 At least 50% pain relief at day 7: 14/17 vs. 3/18 Quality of life: not reported	Level of evidence: unclear risk of bias Computer generated random sequence Unclear allocation concealment Double-blind, but unclear who was blinded Unclear ITT-analysis Cross-over after 7 days: morphine first N=17, placebo first N=18
Peng 2019	Design: RCT Funding: Natural Science Foundation of Hubei Province of China (No. 2017CFB625); CoI: not reported Setting: tertiary hospital, China Sample size: N=60 Duration: recruitment Jun 2015 – Dec 2017	Eligibility criteria: patients with cancer wound pain *A priori* patient characteristics: M/F: 24/36 Mean age: 51.4y	Morphine hydrochloride 10 mg po, 10' before dressing change (N=30) vs. 5% compound lidocaine cream (lidocaine 2.5%, prilocaine 2.5%) 1.5g/10 cm², 10' before dressing change (N=30)	CRITICAL OUTCOMES Pain: VAS: significantly higher scores in morphine group after 20 and 25' Quality of life: Kolcaba comfort scale; significantly higher scores in lidocaine group	Level of evidence: high risk of bias Unclear randomization method, both pseudo-randomisation suspected ("Patients were randomly divided into two groups in chronological order") Unclear allocation concealment, blinding and ITT analysis Pain and comfort data only reported as a figure, no raw data

Abbreviations: 95%CI: 95% confidence interval; CoI: conflict of interest; NRS: numeric rating scale; po: per os; RCT: randomised controlled trial; VAS: visual analogue scale.

References

Adderley UJ, Holt IG. Topical agents and dressings for fungating wounds. Cochrane Database Syst Rev. 2014(5):CD003948.

Ciałkowska-Rysz, A., Dzierżanowski, T. (2019). Topical morphine for treatment of cancer-related painful mucosal and cutaneous lesions: A double-blind, placebo-controlled cross-over clinical trial. Archives of Medical Science, 15(1), 146–151.

Finlayson K, Teleni L, McCarthy AL. Topical Opioids and Antimicrobials for the Management of Pain, Infection, and Infection-Related Odors in Malignant Wounds: A Systematic Review. Oncol Nurs Forum. 2017;44(5):626-32.

Lund-Nielsen B, Adamsen L, Kolmos HJ, Rorth M, Tolver A, Gottrup F. The effect of honey-coated bandages compared with silver-coated bandages on treatment of malignant wounds - a randomized study. Wound Repair and Regeneration 2011;19(6):664-70.

Peng L, Zheng HY, Dai Y. Local dermal application of a compound lidocaine cream in pain management of cancer wounds. Braz J Med Biol Res. 2019;52(11):e8567.

GRADE tabellen – Geïncludeerde studies

Author(s): Lund-Nielsen B, Adamsen L, Kolmos HJ, Rorth M, Tolver A, Gottrup F. The effect of honey-coated bandages compared with silver-coated bandages on treatment of malignant wounds - a randomized study. Wound Repair and Regeneration 2011;19(6):664-70.

Question: Manuka honey-coated dressings compared to silver-coated dressings in patients with advanced stage cancer and malignant wounds

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**manuka honey-coated dressings**	**silver-coated dressings**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain (VAS 100 mm)												
1	randomised trials	serious[a]	not serious	not serious	very serious[b]	none	No significant difference between groups, p= 0.733				⨁◯◯◯ Very low	CRITICAL
Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval

Explanations

a. Lund-Nielsen 2011: unclear allocation concealment and blinding

b. No quantification of precision possible

Author(s): Peng L, Zheng HY, Dai Y. Local dermal application of a compound lidocaine cream in pain management of cancer wounds. Braz J Med Biol Res. 2019;52(11):e8567.

Question: Oral morphine compared to topical lidocaine in patients with cancer wound pain

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**oral morphine**	**topical lidocaine**	**Relative (95% CI)**	**Absolute (95% CI)**		
Pain (VAS)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	Significantly higher scores in morphine group after 20 and 25' (p<0.01)				⊕◯◯◯ Very low	CRITICAL
Kolcaba comfort scale												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	Significantly higher scores in lidocaine group (p<0.01)				⊕◯◯◯ Very low	CRITICAL

CI: confidence interval

Explanations

a. Peng 2019: pseudo-RCT, unclear methodology

b. Only reported in a figure (no raw data)

Author(s): Ciałkowska-Rysz, A., Dzierżanowski, T. (2019). Topical morphine for treatment of cancer-related painful mucosal and cutaneous lesions: A double-blind, placebo-controlled cross-over clinical trial. Archives of Medical Science, 15(1), 146–151.

Question: Topical morphine compared to placebo in patients with cancer-related painful mucosal and cutaneous lesions

Setting:

Bibliography:

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**topical morphine**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mean pain intensity (NRS 0-10): day 7												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2.5 (95%CI 1.6-3.3) vs. 4.6 (3.3-5.9), p<0.0001				⊕⊕◯◯ Low	CRITICAL
Mean pain intensity (NRS 0-10): day 14												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2.5 (1.6-3.4) vs. 5.2 (4.4-6.1), p<0.0001				⊕⊕◯◯ Low	CRITICAL
Pain relief: % change from baseline in pain intensity												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	57% vs. 16%, p=0.0000004				⊕⊕◯◯ Low	CRITICAL
At least 50% pain relief at day 7												
1	randomised trials	serious[a]	not serious	not serious	not serious	none	14/17 (82.4%)	3/18 (16.7%)	**RR 4.94** (1.72 to 14.21)	**657 more per 1.000** (from 120 more to 1.000 more)	⊕⊕⊕◯ Moderate	CRITICAL

Quality of life - not measured												
-	-	-	-	-	-	-	-	-	-	-	-	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a. Ciałkowska-Rysz 2019: unclear allocation concealment and ITT analysis

b. CI around estimated SMD includes -0.5

c. No quantification of difference (no CI around MD)