

The efficacy of cryotherapy compared to other modalities in the management of palmoplantar warts: a systematic review and network meta-analysis

Anwar R. Alrashidi,¹ Esraa Shaheen,^{2,3} Amal Abualola,^{2,3} Alanoud A. Alharkan,⁴ Abdulaziz Aljuaid,^{2,3} Khalid M. Alshareef,^{2,3} Abdullah A. Ghaddaf,^{2,3} Samer Alamri,⁵ Sahal J. Samarkandy^{2,3,5}

¹Department of Dermatology, King Fahad Medical City, Riyadh; ²College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah; ³King Abdullah International Medical Research Center, Jeddah;

⁴Department of Family Medicine, King Abdulaziz Medical City, National Guard Hospital, Riyadh; ⁵Department of Dermatology, King Abdulaziz Medical City, Jeddah, Saudi Arabia

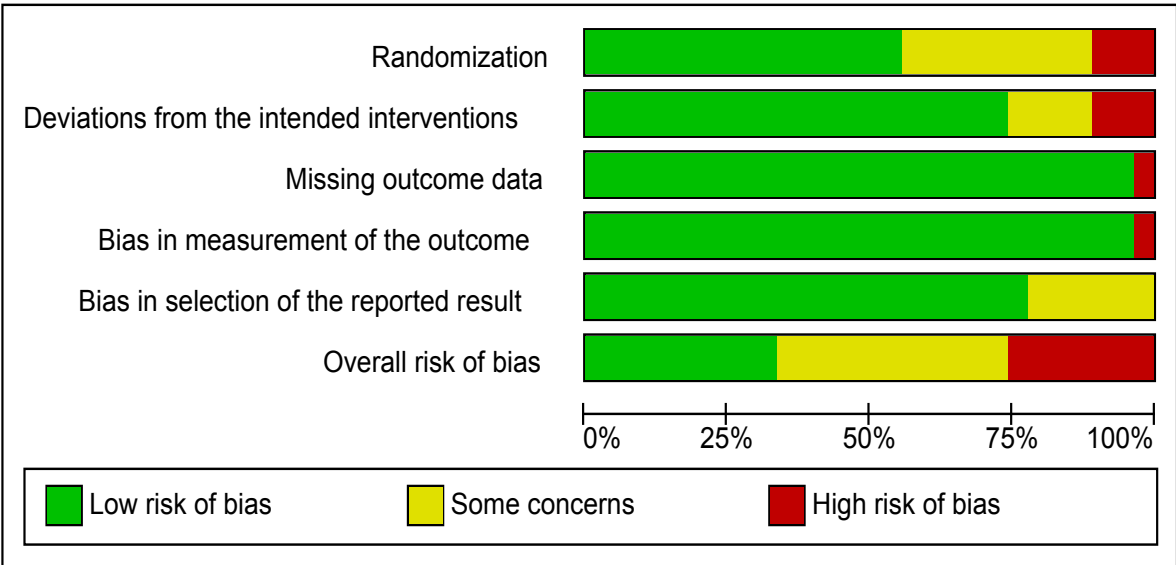
SUPPLEMENTARY MATERIAL

Search strategy for Medline, Embase, CENTRAL, and Scopus last performed on March 1st, 2023

(n=871):

1. Plantar warts\$.mp.
2. Palmoplantar warts\$.mp.
3. 1 or 2
4. Therapeutics/
5. Therapeutics\$.mp.
6. Treatment\$.mp.
7. Cryotherapy/
8. Cryotherapy\$.mp.
9. exp Bleomycin/
10. Bleomycin\$.mp.
11. exp Radiofrequency Ablation/
12. Radiofrequency Ablation\$.mp.
13. Thermotherapy\$.mp.
14. Trichloroacetic Acid/
15. Trichloroacetic Acid\$.mp.
16. Salicylic Acid/
17. Salicylic Acid\$.mp.
18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. exp Randomized Controlled Trial/ or exp Clinical Trial/
20. Trial\$.mp.
21. 19 or 20
22. 3 and 18 and 21

Supplementary Figure 1. Risk of bias graph.



Supplementary Figure 2. Risk of bias summary.

	Randomization	Deviations from the intended interventions	Missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
Abdel-latif, 2020	?	+	+	+	+	?
Abd El-Magiud, 2020	+	?	+	+	+	?
Adalatkah, 2007	?	+	+	+	?	-
Ahmed, 2018	+	+	+	+	?	?
Albalat, 2020	?	?	+	+	+	?
Ali, 2022	?	+	+	+	+	?
Amar, 2020	+	+	+	+	+	+
Anwar, 2021	?	+	+	+	?	-
Arora, 2014	?	+	+	+	+	?
Attwa 2020	-	+	+	+	+	-
Boroujeni, 2018	+	+	+	+	+	+
Bruggink, 2010	+	+	+	+	+	+
Bruggink 2015	+	?	+	+	+	?
Cengiz, 2016	?	+	+	+	+	?
Cockayne, 2011	+	+	+	+	+	+
Cunningham, 2014	+	+	+	-	+	-
Firouzabadi, 2017	+	+	+	+	+	+
Gibson, 1983	-	-	+	+	?	-
Hafeez L., 2021	+	?	+	+	+	?
Kacar, 2011	-	-	+	+	?	-
Karrabi, 2020	+	+	+	+	+	+
Liu, 2020	+	+	+	+	+	+
Maj, 2022	+	+	+	+	+	+
Meymandi, 2017	+	+	+	+	+	+
Muhammed, 2019	+	+	+	+	?	?
Siddiqui, 2022	?	+	+	+	+	?
Stefanaki, 2015	?	-	-	+	+	-

Supplementary Table 1. Characteristics of the included studies.

Study, Year	Study arms	Number of warts		Gender				Mean age		Number of treatment sessions		Follow up/evaluation period		The desired outcomes reported
		Intervention	Control	Intervention		Control		Intervention	Control	Intervention	Control	Intervention		
				Male	Female	Male	Female							
Abd El-Magiud, 2020	Arm 1: Intralesional injection of measles, mumps, and rubella (MMR) vaccine (n=10) Arm 2: Cryotherapy (n=10)	10.45 (±8.49)	7.75 (±3.84)	NR	NR	NR	NR	25.20 (±6.03)	28.00 (±8.81)	Every 2 weeks for all patients until complete resolution or for a maximum of three sessions	Every 2 weeks for all patients until complete resolution or for a maximum of three sessions	4 weeks after treatment	4 weeks after treatment	Cure/response rate
Abdel-latif, 2020	Arm 1: Silver Duct tape (n=50) Arm 2: Cryotherapy (n=50)	2.34 (± 1.26)	2.30 (±1.45)	46 (92%)	4 (8%)	45 (90%)	5 (10%)	30.75 (±8.11)	31.6 (±10.33)	The treatment was applied for 6 days a week and repeated until disappearance of warts or for a maximum of 8 weeks	One session every 2-3 weeks for a maximum of 4 sessions	8 weeks (end of treatment)	8 weeks (end of treatment)	Cure/response rate and adverse events
Adalatkah, 2007	Arm 1: 0.05% intralesional bleomycin (n=44) Arm 2: Cryotherapy spray (n=44)	NR	NR	Male: 42 (47.7 %) Female: 46 (52.3%)				20.2 (±6.9)	20.2 (±6.9)	Every 15 days up to a maximum of three sessions	Every 15 days up to a maximum of three sessions	6 weeks (end of treatment)	6 weeks (end of treatment)	Cure/response rate and adverse events
Ahmed, 2018	Arm 1: Topical 10% formaldehyde soaks (n=13) Arm 2: Cryotherapy spray (n=15)	Single: 1 (7.69%) Multiple: 12 (92.31%)	Single: 0 (0%) Multiple: 15 (100%)	10 (76.93%)	3 (23.07%)	12 (80%)	3 (20%)	18.4 (±9.4)	22.9 (±12.9)	Twice daily for a maximum of 12 weeks	Every 2 weeks for a maximum of 12 weeks or until clearance, whichever was shorter	3 months after treatment	3 months after treatment	Cure/response rate
Albalat, 2020	Arm1: Intralesional cryotherapy (n=65) Arm 2: Cryotherapy spray (n=65)	NR	NR	47 (72.3%)	18 (27.7%)	46 (70.8%)	19 (29.2%)	38.34 (±12.72)	36.97 (±11.64)	One session at 2 weeks intervals until complete clearance or for a maximum of 5 sessions	One session at 2 weeks intervals until complete clearance or for a maximum of 5 sessions	6 months after treatment	6 months after treatment	Cure/response rate, pain score, recurrence rate, and adverse events
Ali, 2022	Arm 1: 50% Topical salicylic acid + Cryotherapy (n=35) Arm 2: Cryotherapy alone (n=35)	NR	NR	19 (54.28%)	16 (45.72%)	19 (54.28%)	16 (45.72%)	24.91 (±4.21)	22.97 (±5.39)	NR	Every 2-3 weeks for 12 weeks	12 weeks (end of treatment)	12 weeks (end of treatment)	Cure/response rate
Amar, 2020	Arm 1: 0.1% topical Adapalene gel (n=37) Arm 2: Cryotherapy (n=37)	1 wart: 7 (18.91%) 2 warts: 21 (56.75%) 3 warts: 9 (24.32%)	1 wart: 7 (18.91%) 2 warts: 18 (48.64%) 3 warts: (32.43%)	29 (78.4%)	8 (21.6%)	25 (67.6%)	12 (32.4%)	26.95 (±9.39)	27.14 (±9.62)	Daily patient self-treatment for 8 weeks	Two sessions at 3 weekly intervals.	8 weeks (end of treatment)	8 weeks (end of treatment)	Cure/response rate

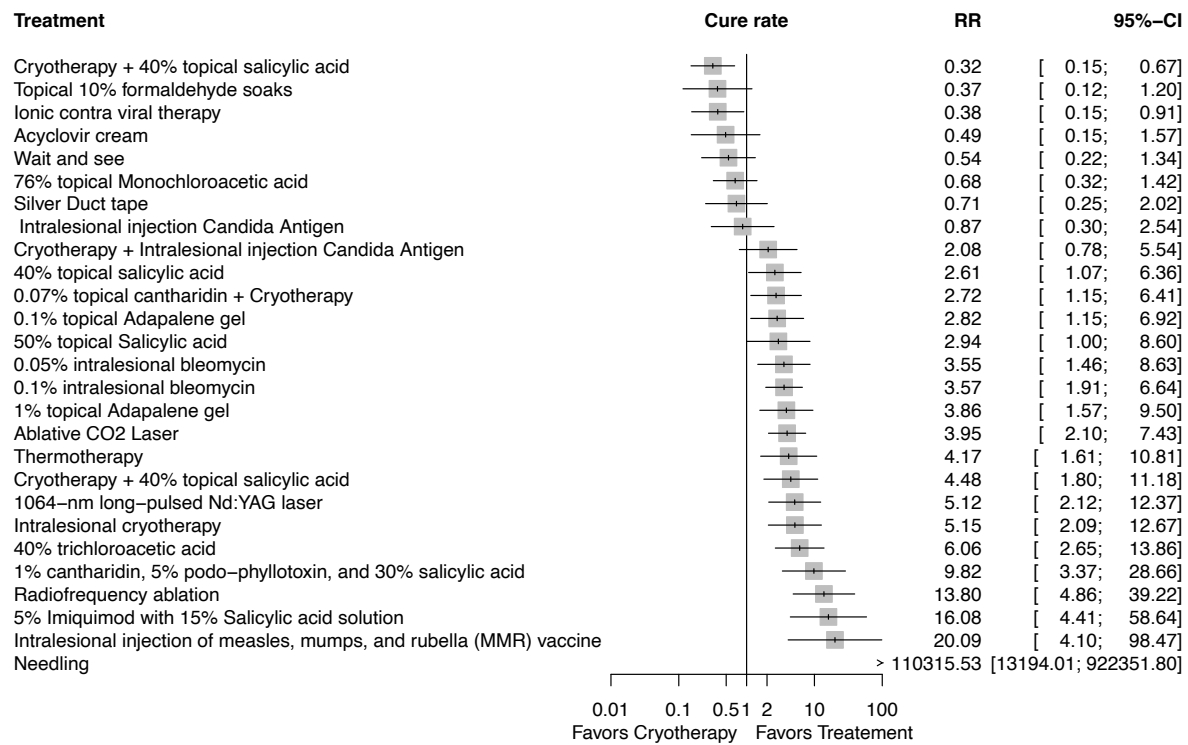
Anwar, 2021	Arm 1: Ablative CO2 Laser (n=60) Arm 2: Cryotherapy spray (n=60)	NR	NR	38 (63.33%)	22 (36.67%)	40 (66.67%)	20 (33.33%)	32.0 (±10.99)	31.63 (±10.64)	Once a week until clearing of all lesions or until a maximum of 8 weeks	Once a week until clearing of all lesions or until a maximum of 8 weeks	8 weeks after treatment	8 weeks after treatment	Cure/response rate
Arora, 2014	Arm 1: Radiofrequency ablation (n=25) Arm 2: Cryotherapy (n=25)	5.28 (±4.96)	3.40 (±2.61)	12 (48%)	13 (52%)	14 (56%)	11 (44%)	29.36 (±13.54)	33.16 (±17.77)	Average of 3 sessions	Average of 5.63 sessions	12 weeks (end of treatment)	12 weeks (end of treatment)	Cure/response rate and adverse events
Attwa, 2020	Arm 1: Intralesional injection Candida Antigen (n=20) Arm 2: Cryotherapy (n=20) Arm 3: Cryotherapy + Intralesional injection Candida Antigen (n=20)	Arm 1: 11.70 (±10.42) Arm 3: 16.40 (±18.03)	4.65 (±1.87)	Arm 1: 6 (30%) Arm 3: 9 (45%)	Arm 1: 14 (70%) Arm 3: 11 (55%)	10 (50%)	10 (50%)	Arm 1: 35.35 (±13.89) Arm 3: 32.85 (±10.79)	28.05 (±7.45)	Arm 1: One session every 2 weeks for a maximum of 5 sessions Arm 3: One session every 2 weeks for a maximum of 5 sessions	One session every 2 weeks for a maximum of 5 sessions	3 months after treatment	3 months after treatment	Cure/response rate, patient satisfaction, recurrence rate, and adverse events
Boroujeni, 2018	Arm 1: Ablative CO2 Laser (n=29) Arm 2: Cryotherapy spray (n=27)	Median (range): 5 (1-20)	Median (range): 1 (1-20)	10 (34%)	19 (66%)	15 (56%)	12 (44%)	Median (range): 27 (18-75)	Median (range): 25 (18-53)	Median (range): 1 session (1-2 sessions)	Median (range): 3 sessions (1-12 sessions)	3 months after treatment	3 months after treatment	Cure/response rate and recurrence rate
Bruggink, 2010	Arm 1: 40% topical salicylic acid (n=44) Arm 2: Cryotherapy (n=39) Arm 3: Wait and see (n=45)	NR	NR	NR	NR	NR	NR	NR	NR	Daily patient self-treatment for a maximum of 13 weeks	One session every two weeks for a maximum of 13 weeks	13 weeks (end of treatment)	13 weeks (end of treatment)	Cure/response rate and adverse events
Bruggink 2015 (1)	Arm 1: 76% topical Monochloroacetic acid (n=109) Arm 2: Cryotherapy + 40% topical salicylic acid (n=118)	Median (IQR): 2 (1-4)	Median (IQR): 1 (1-3)	40 (37%)	69 (63%)	42 (36%)	76 (64%)	Median (IQR): 10 (7-29)	Median (IQR): 11 (6-38)	76% topical Monochloroacetic acid was applied every 2 weeks until all warts were completely cured or for a maximum of 13 weeks	Cryotherapy was applied every 2 weeks + daily patient self-treatment until all warts were completely cured or for a maximum of 13 weeks	13 weeks (end of treatment)	13 weeks (end of treatment)	Cure/response rate, pain score, and adverse events
Bruggink 2015 (2)	Arm 1: 76% topical Monochloroacetic acid (n=94) Arm 2: Cryotherapy (n=94)	Median (IQR): 1 (1-3)	Median (IQR): 2 (1-4)	40 (43%)	54 (57%)	51 (45%)	43 (46%)	Median (IQR): 14 (9-44)	Median (IQR): 16 (8-42)	76% topical Monochloroacetic acid was applied every 2 weeks until all warts were completely cured or for a maximum of 13 weeks	Cryotherapy was applied every 2 weeks until all warts were completely cured or for a maximum of 13 weeks	13 weeks (end of treatment)	13 weeks (end of treatment)	Cure/response rate, pain score, and adverse events

Cengiz, 2016	Arm 1: 40% trichloroacetic acid solution (n=30) Arm 2: Cryotherapy (n=30)	NR	NR	13 (43.33%)	17 (56.67%)	15 (50%)	15 (50%)	20.03 (±12.12)	25.16 (±9.04)	One session every 2 weeks for a maximum of 4 sessions	One session every 2 weeks for a maximum of 4 sessions	8 weeks after treatment	4 weeks after treatment	Cure/response rate, recurrence rate,, and adverse events
Cockayne, 2011	Arm 1: 50% topical Salicylic acid (n=123) Arm 2: Cryotherapy spray (n=117)	3.4 (±3.6)	4.0 (±6.6)	50 (41%)	73 (59%)	31 (26%)	86 (74%)	30.2 (±16.4)	30.1 (±15.7)	Daily patient self-treatment for a maximum of 8 weeks	Every 2-3 weeks up to 4 sessions	6 months after treatment	6 months after treatment	Cure/response rate, patient satisfaction, and adverse events
Cunningham, 2014	Arm 1: Needling (n=18) Arm 2: Cryotherapy (n=19)	4.17 (±3.68)	2.58 (±2.71)	10 (56%)	8 (44%)	11 (58%)	8 (42%)	26.11 (±9.99)	30.37 (±12.65)	One session every 2 weeks for a maximum of 3 sessions	One session every 2 weeks for a maximum of 3 sessions	6 weeks after treatment	6 weeks after treatment	Cure/response rate and adverse events
Firouzabadi, 2017	Arm 1: Thermotherapy (n=26) Arm 2: Cryotherapy (n=26)	2.69 (±2.09)	3.19 (±2.76)	20 (76.9%)	6 (23.1%)	14 (53.8%)	12 (46.2%)	30.08 (±9.94)	27.46 (±7.82)	1 session	Every 2-3 weeks up to six sessions if required	3 months after treatment	3 months after treatment	Cure/response rate and adverse events
Gibson, 1983	Arm 1: Acyclovir cream (n=18) Arm 2: Cryotherapy spray (n=11)	NR	NR	NR	NR	NR	NR	NR	NR	Once daily for 6 weeks	4 sessions	8 weeks (end of treatment)	8 weeks (end of treatment)	Cure/response rate
Hafeez L., 2021	Arm 1: 0.1% intralesional bleomycin (n=51) Arm 2: Cryotherapy (n= 51)	1.90 (±1.08)	1.78 (±1.25)	37 (72.5%)	14 (27.5%)	23 (45.1%)	28 (54.9%)	24.61 (±7.76)	24.39 (±7.7)	Two sessions at 3-week intervals.	Two sessions at 3-week intervals.	6 weeks (end of treatment)	6 weeks (end of treatment)	Cure/response rate
Kacar, 2011	Arm 1: 1% cantharidin, 5% podo-phyllotoxin, and 30% salicylic acid (n=14) Arm 2: Cryotherapy spray (n= 12)	5.36 (±4.03)	4.91 (±4.54)	7 (50%)	7 (50%)	5 (41.7%)	7 (58.3%)	25.71 (±8.08)	23.92 (±6.71)	5 sessions	5 sessions	NR	NR	Cure/response rate, pain score, and adverse events
Karrabi, 2020	Arm 1: 40% trichloroacetic acid (n=30) Arm 2: Cryotherapy cotton tip applicator (n=30)	NR	NR	19 (46.34%)	11 (53.66%)	22 (53.66%)	8 (46.34%)	24.03 (±12.11)	25.16 (±8)	4 sessions within 4 weeks	4 sessions Within 8 weeks	6 months after treatment	6 months after treatment	Cure/response rate and adverse events

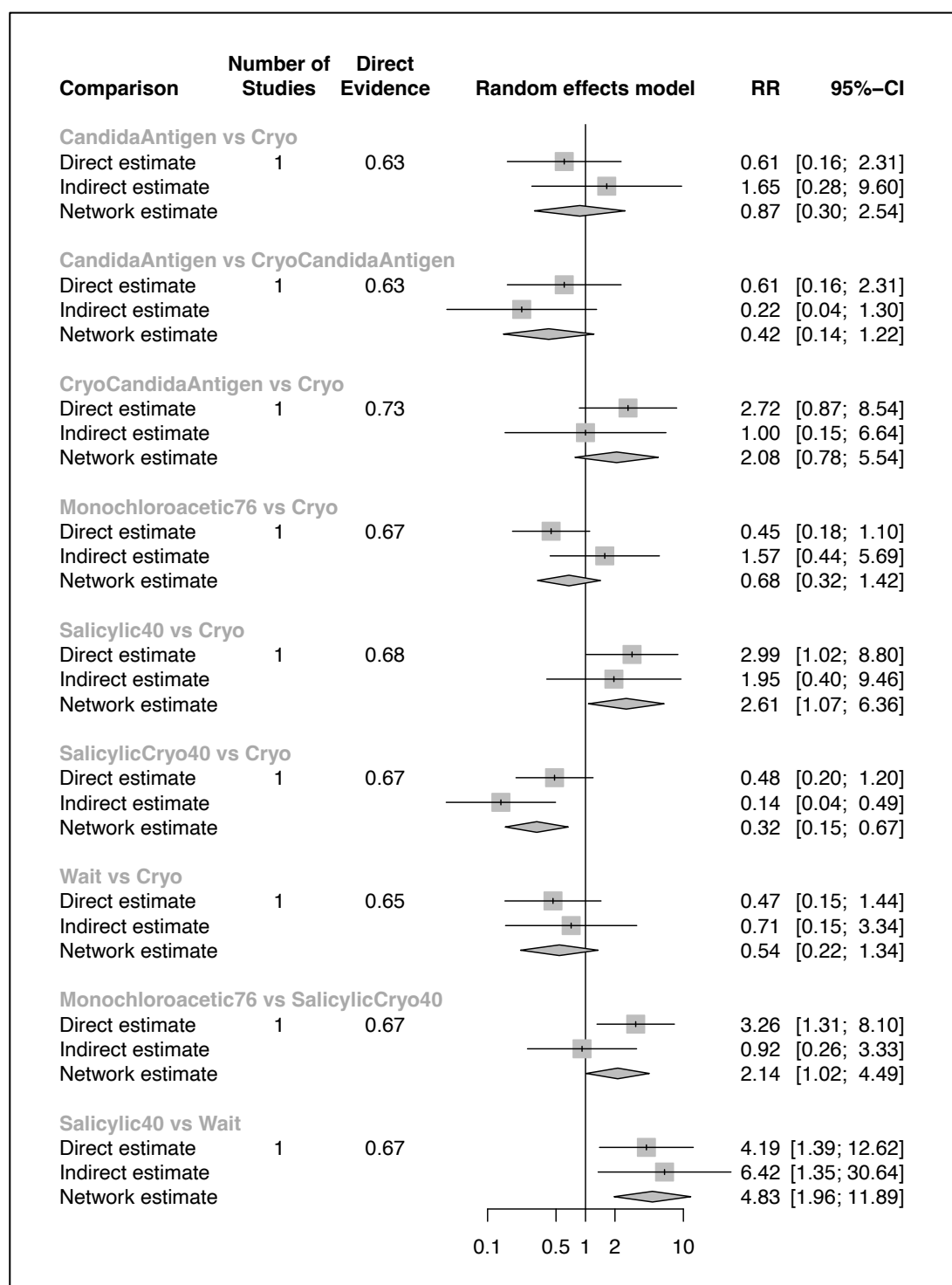
Supplementary Table 2. Ranking for cure rate.

Topical agent	Full name	P-score	Sample size
Needling	Needling	1.0000	18
MMR	Intralesional injection of measles, mumps, and rubella (MMR) vaccine	0.9058	10
ImiquimodSalicylic	5% Imiquimod with 15% Salicylic acid solution	0.8945	18
Radio	Radiofrequency ablation	0.8859	25
Canpodosalicylic	1% cantharidin, 5% podophyllotoxin, and 30% salicylic acid	0.8332	14
Trichloroacetic	40% trichloroacetic acid	0.7364	60
IntralesionalCryo	Intralesional cryotherapy	0.6866	65
LaserYAG	1064-nm long-pulsed Nd:YAG laser	0.6854	75
SalicylicCryo50	50% Topical salicylic acid + Cryotherapy	0.6438	35
Thermo	Thermotherapy	0.6210	26
LaserCO2	Ablative CO2 Laser	0.6054	89
Adapalene1	1% topical Adapalene gel	0.5965	37
Bleomycin0.1	0.1% intralesional bleomycin	0.5690	131
Bleomycin0.05	0.05% intralesional bleomycin	0.5690	44
Salicylic50	50% topical Salicylic acid	0.5151	123
Adapalene0.1	0.1% topical Adapalene gel	0.4985	37
CanCryo	0.07% topical cantharidin + Cryotherapy	0.5151	55
Salicylic40	40% topical salicylic acid	0.4756	44
CryoCandidaAntigen	Cryotherapy + Intralesional injection Candida Antigen	0.4194	20
Cryo	Cryotherapy	0.2613	1112
CandidaAntigen	Intralesional injection Candida Antigen	0.2310	20
Ducttape	Silver Duct tape	0.1937	50
Monochloroacetic76	76% topical Monochloroacetic acid	0.1855	203
Wait	Wait and see	0.1431	45
Acyclovir	Acyclovir cream	0.1311	19
Formaldehyde	Topical 10% formaldehyde soaks	0.0891	13
Contraviral	Ionic contra viral therapy	0.0832	40
SalicylicCryo40	Cryotherapy + 40% topical salicylic acid	0.0539	118
Bold indicates significant P-score			

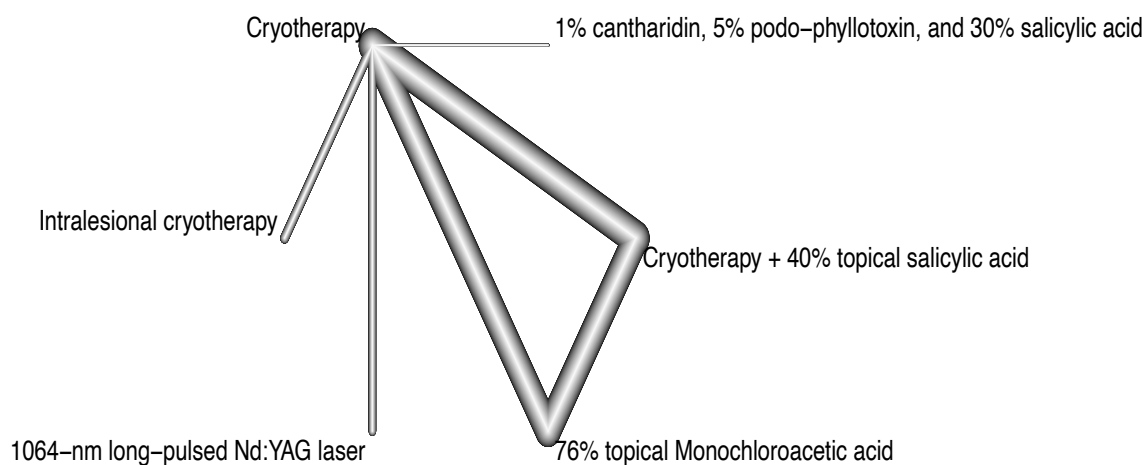
Supplementary Figure 3. Cure Forest plot pooled.



Supplementary Figure 4. Forest plot net split for cure rate.



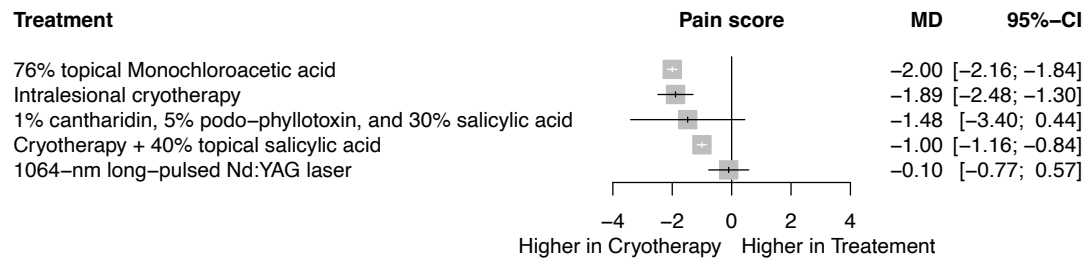
Supplementary Figure 5. Network graph for pain score.



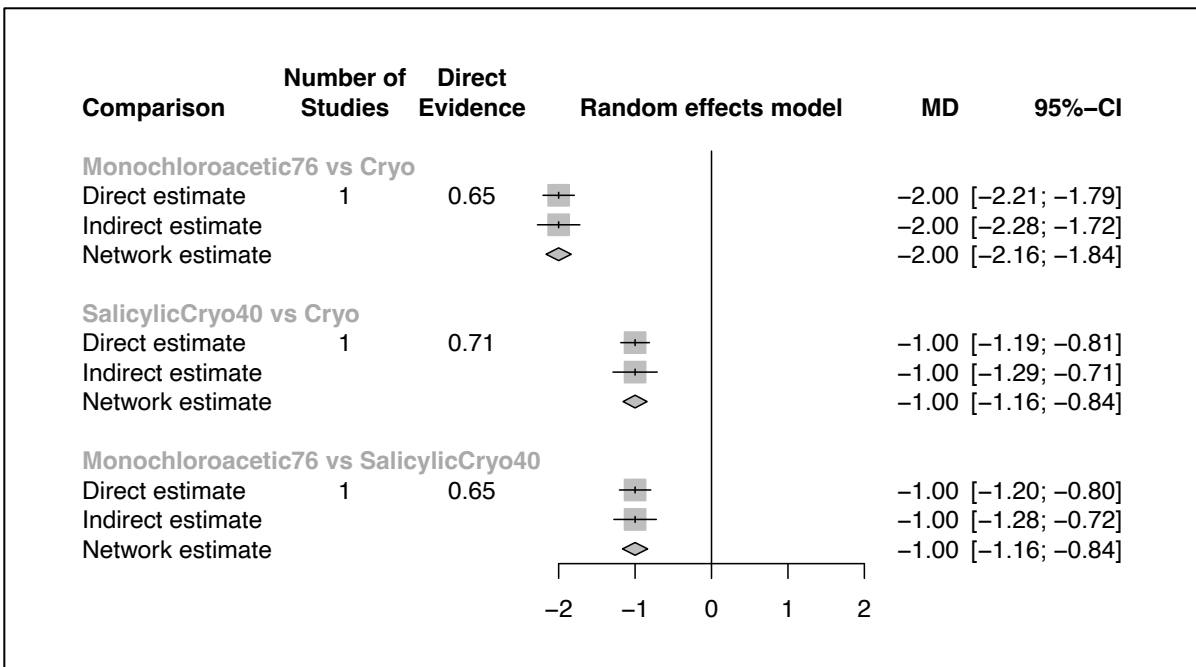
Supplementary Table 3. Ranking for pain score.

Topical agent	Full name	P-score	Sample size
Cryo	Cryotherapy	0.9098	1112
LaserYAG	1064-nm long-pulsed Nd:YAG laser	0.8576	75
SalicylicCryo40	Cryotherapy + 40% topical salicylic acid	0.5380	118
Canpodosalicylic	1% cantharidin, 5% podo-phyllotoxin, and 30% salicylic acid	0.3655	14
IntralesionalCryo	Intralesional cryotherapy	0.1969	65
Monochloroacetic76	76% topical Monochloroacetic acid	0.1323	203
Bold indicates significant P-score			

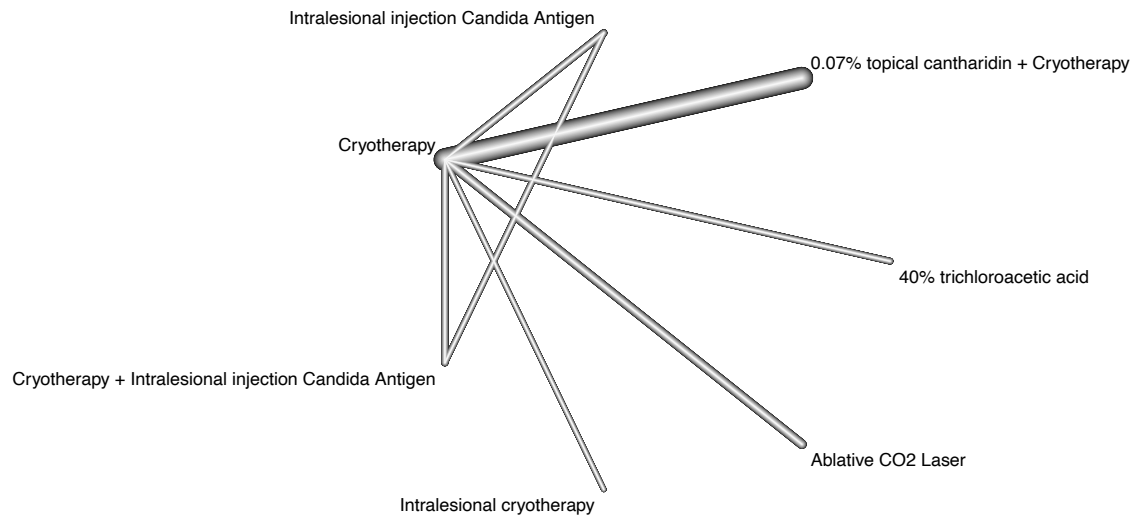
Supplementary Figure 6. Pain Forest plot pooled.



Supplementary Figure 7. Forest plot net split for pain score.



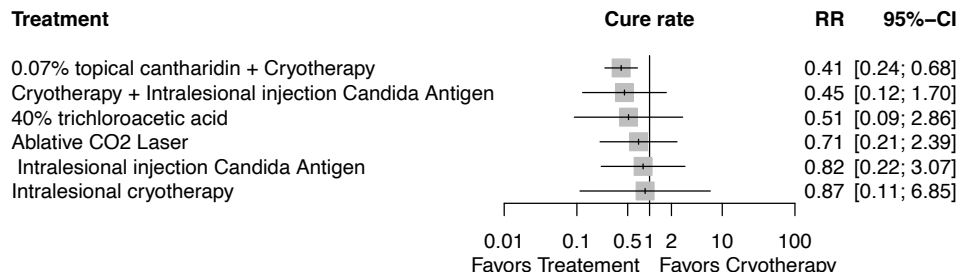
Supplementary Figure 8. Network graph for recurrence rate.



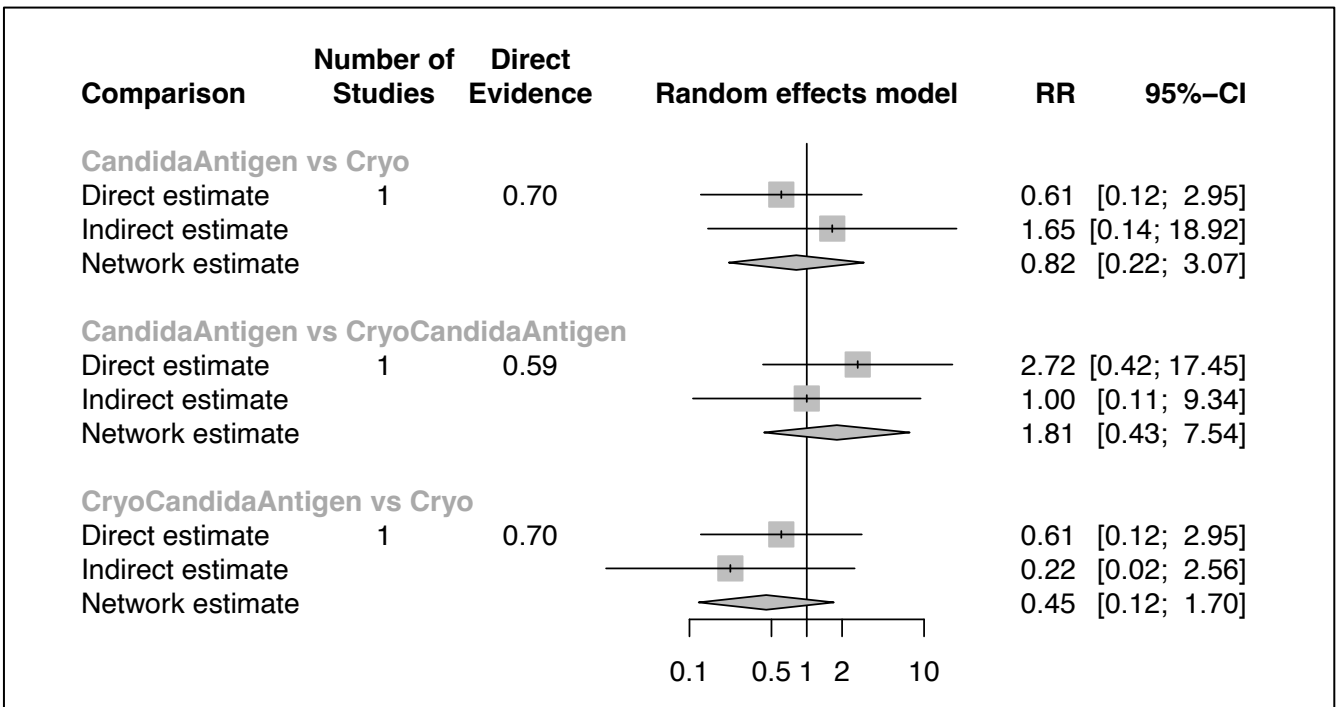
Supplementary Table 4. Ranking for recurrence rate.

Topical agent	Full name	P-score	Sample size
Cryo	Cryotherapy	0.7569	1112
CandidaAntigen	Intralesional injection Candida Antigen	0.6179	20
IntralesionalCryo	Intralesional cryotherapy	0.6070	65
LaserCO2	Ablative CO2 Laser	0.5421	89
Trichloroacetic	40% trichloroacetic acid	0.4071	60
CryoCandidaAntigen	Cryotherapy + Intralesional injection Candida Antigen	0.3256	20
CanCryo	0.07% topical cantharidin + Cryotherapy	0.2435	55
Bold indicates significant P-score			

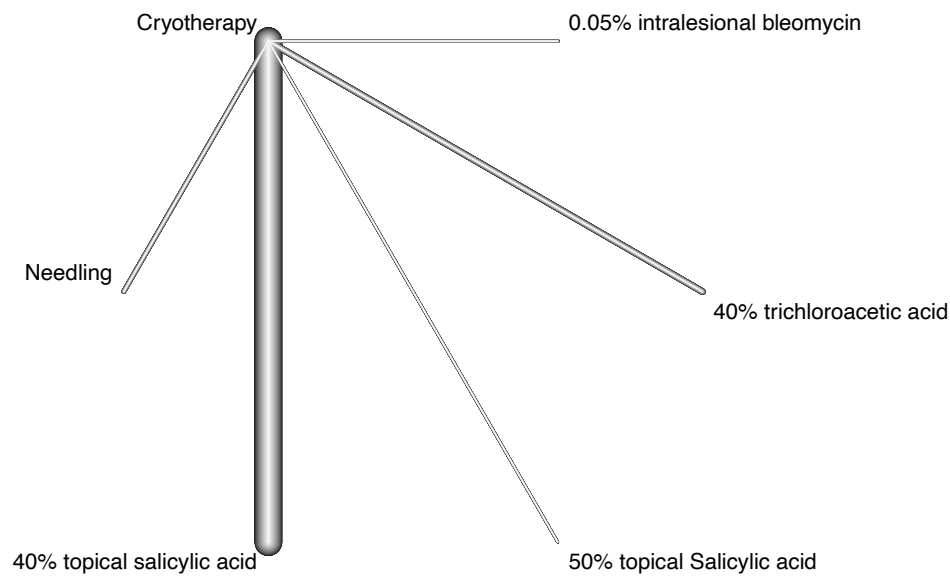
Supplementary Figure 9. Recurrence rate forest plot pooled.



Supplementary Figure 10. Forest plot net split for recurrence rate.



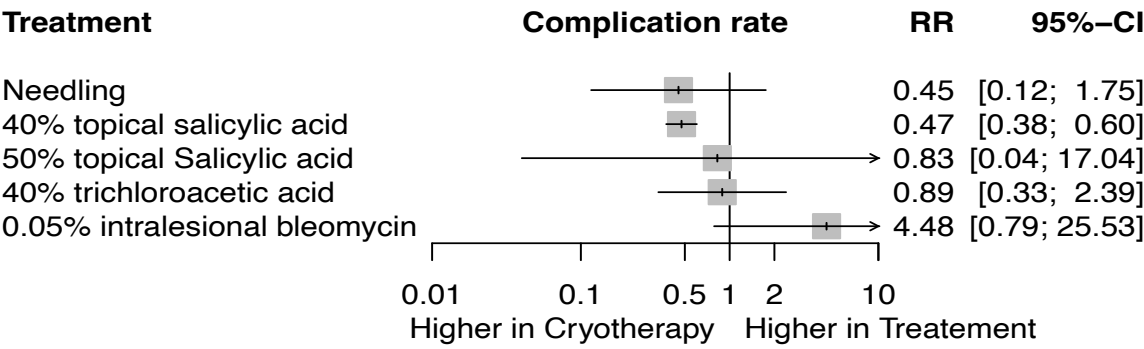
Supplementary Figure 11. Network graph for complication rate.



Supplementary Table 5. Ranking for complication rate.

Topical agent	Full name	P-score	Sample size
Bleomycin0.05	0.05% intralesional bleomycin	0.9399	44
Cryo	Cryotherapy	0.6119	1112
Trichloroacetic	40% trichloroacetic acid	0.5318	60
Salicylic50	50% topical Salicylic acid	0.4765	123
Needling	Needling	0.2389	18
Salicylic40	40% topical salicylic acid	0.2010	44
Bold indicates significant P-score			

Supplementary Figure 12. Complications Forest plot pooled.



Supplementary Table 6. Details of treatment-related adverse events.

Study	Topical agent	Pruritus			Dryness			Face burning or stinging			Worsening of baseline rosacea			Headache		
		Events	Sample size	%	Events	Sample size	%	Events	Sample size	%	Events	Sample size	%	Events	Sample size	%
Gold 2020 (study 11)	Topical Minocycline 1.5% once daily	15	423	3.50%	16	423	3.70%	16	423	3.80%	NR	NR	NR	NR	NR	NR
	Topical vehicle once daily	10	225	4.40%	11	225	4.90%	3	225	1.30%	NR	NR	NR	NR	NR	NR
Gold 2020 (study 12)	Topical Minocycline 1.5% once daily	15	474	3.20%	21	474	4.40%	9	474	1.90%	NR	NR	NR	NR	NR	NR
	Topical vehicle once daily	5	235	2.10%	13	235	5.50%	3	235	1.30%	NR	NR	NR	NR	NR	NR
Carmichael 1993	Topical Azelaic acid 20% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bleicher 1987	Topical Metronidazole 0.75% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Elewski 2003	Topical Azelaic acid gel 15% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical Metronidazole gel 0.75% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Maddin 1999	Topical Azelaic acid 20% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical Metronidazole 0.75% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Bitar 1990	Topical Metronidazole 1% twice daily	3	50	6%	1	50	2%	NR	NR	NR	NR	NR	NR	0	50	0%
	Topical vehicle twice daily	2	50	4%	0	50	0%	NR	NR	NR	NR	NR	NR	1	50	1%
Webster 2020	Topical Minocycline gel 1% twice daily	1	92	1.09%	NR	NR	NR	NR	NR	NR	0	92	0%	0	92	0%
	Topical Minocycline gel 3% twice daily	1	96	1.04%	NR	NR	NR	NR	NR	NR	1	96	1.04%	1	96	1.04%
Draclos 2015	Topical vehicle twice daily	0	82	0%	NR	NR	NR	NR	NR	NR	1	82	1.22%	0	82	0%
	Topical Azelaic acid gel 15% twice daily	7	484	1.40%	5	484	1%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mrowietz 2018	Topical vehicle twice daily	2	477	0.40%	3	477	0.60%	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical Minocycline gel 1.5% once daily	0	79	0%	NR	NR	NR	0	79	0%	0	79	0%	0	79	0%
Draclos 2013	Topical minocycline gel 3% once daily	0	75	0%	NR	NR	NR	0	75	0%	2	75	2.70%	2	75	2.70%
	Topical vehicle once daily	1	78	1.30%	NR	NR	NR	1	78	1 (1.3%)	0	78	0%	0	78	0%
	Topical Azelaic acid foam 15% twice daily	3	198	1.50%	NR	NR	NR	3	198	1.50%	1	198	0.50%	NR	NR	NR

[illegible][illegible]

[illegible]

	20% cream twice daily												
	Topical vehicle twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thiboutot 2003 (Study 1)	Azelaic Acid gel 15% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Thiboutot 2003 (Study 2)	Azelaic Acid gel 15% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kocak 2002	Topical Metronidazole 0.75% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Taieb 2014	Topical Ivermectin 1% cream twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical Metronidazole 0.75% twice daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miyachi 2021	Topical Metronidazole gel 0.75% twice daily	NR	NR	NR	1	65	1.50%	3	65	4.60%	NR	NR	NR
	Topical vehicle gel twice daily	NR	NR	NR	0	65	0%	1	65	2%	NR	NR	NR
Gold 2014 (study 1)	Topical Ivermectin 1% once daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle once daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gold 2014 (study 2)	Topical Ivermectin 1% once daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle once daily	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Solomon 2014	Topical Azelaic acid foam 15% twice daily	17	483	3.50%	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vechile twice daily	6	478	1.30%	NR	NR	NR	NR	NR	NR	NR	NR	NR
Aronson 1987	Topical Metronidazole gel 0.75%	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	Topical vehicle gel	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Total		58	2323	2.50%	7	362	1.93%	27	362	7.46%	2	671	0.30%