

Appendix S1. Search strategies

MEDLINE

1. vitiligo[TIAB] 5637
2. "Vitiligo"[Mesh] 4439
3. 1 OR 2 6173
4. (fractional[TIAB] OR "carbon dioxide"[TIAB] OR CO2[TIAB] OR Gas[TIAB]) AND (laser[TIAB] OR Lasers[TIAB]) 15546
5. "Lasers, Gas"[Mesh] 1621
6. 4 OR 5 16151
7. 3 AND 6 45

EMBASE

1. vitiligo:ab,ti 7638
2. "vitiligo"/exp 9504
3. 1 OR 2 10272
4. fractional:ab,ti OR "carbon dioxide":ab,ti OR co2:ab,ti OR gas:ab,ti AND (laser:ab,ti OR lasers:ab,ti) 11249
5. "gas laser"/de OR "carbon dioxide laser"/exp 8361
6. 4 OR 5 16616
7. 3 AND 6 90

COCHRANE

1. vitiligo:ti,ab,kw 476
2. MeSH descriptor: [Vitiligo] explode all trees 194
3. 1 OR 2 476
4. (fractional OR "carbon dioxide" OR CO2 OR Gas) and (laser OR Lasers):ti,ab,kw 894
5. MeSH descriptor: [Lasers, Gas] explode all trees 142
6. 4 OR 5 894
7. 3 AND 6 16

SCOPUS

1. TITLE-ABS (vitiligo) 7076
2. INDEXTERMS (vitiligo) 8059
3. 1 OR 2 9680
4. TITLE-ABS ((fractional OR "carbon dioxide" OR co2 OR gas) AND (laser OR lasers)) 94054
5. INDEXTERMS ("Lasers, Gas") 7111
6. 4 OR 5 97789
7. 3 AND 6 52

Web of Science

1. TOPIC: (vitiligo) AND TITLE: (vitiligo) 4238
2. TOPIC: ((fractional OR "carbon dioxide" OR CO2 OR Gas) AND (laser OR Lasers)) AND TITLE: ((fractional OR "carbon dioxide" OR CO2 OR Gas) AND (laser OR Lasers)) 20185
3. 1 AND 2 19

MEDLINE 45

EMBASE 90

COCHRANE 16

SCOPUS 52

Web of Science 19

Total 222

Duplicates 87

Final 135

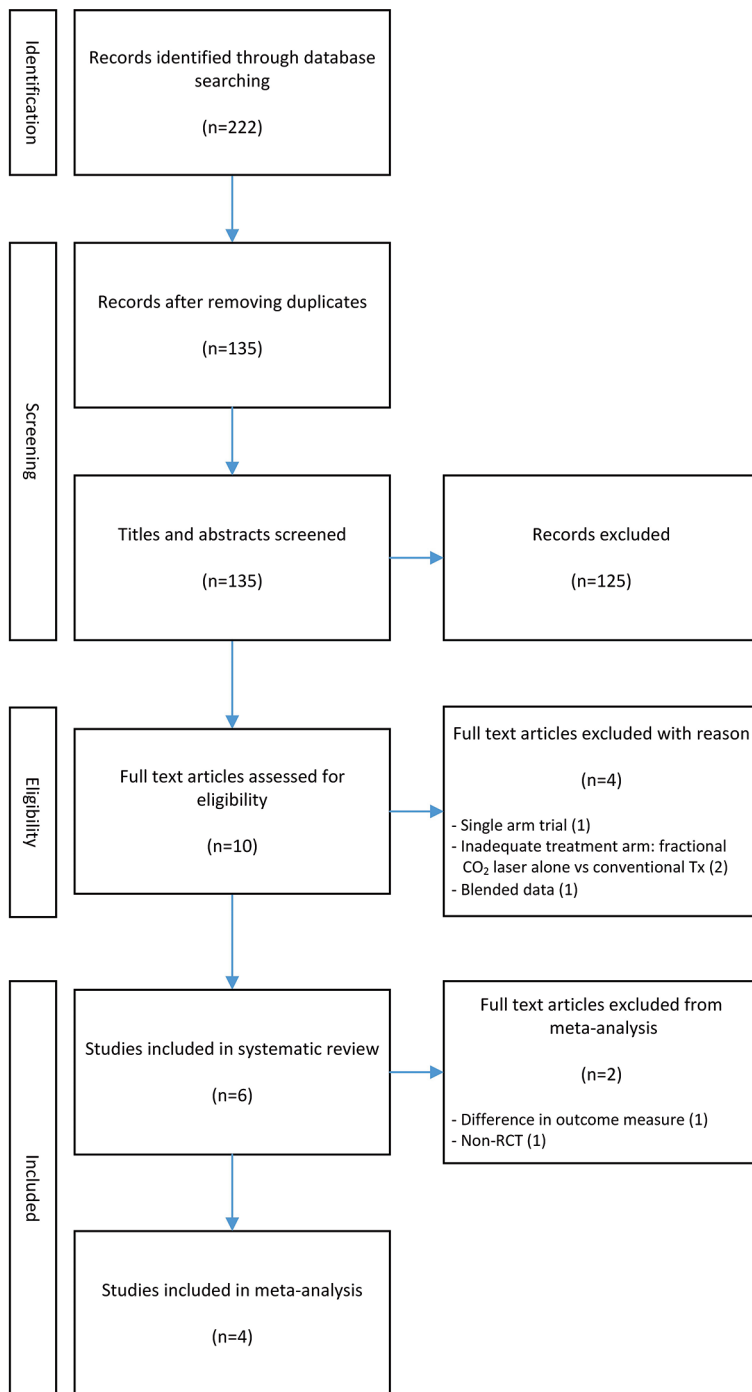


Fig S1. Fractional carbon dioxide (CO₂) laser as an add-on treatment for vitiligo. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flowchart.

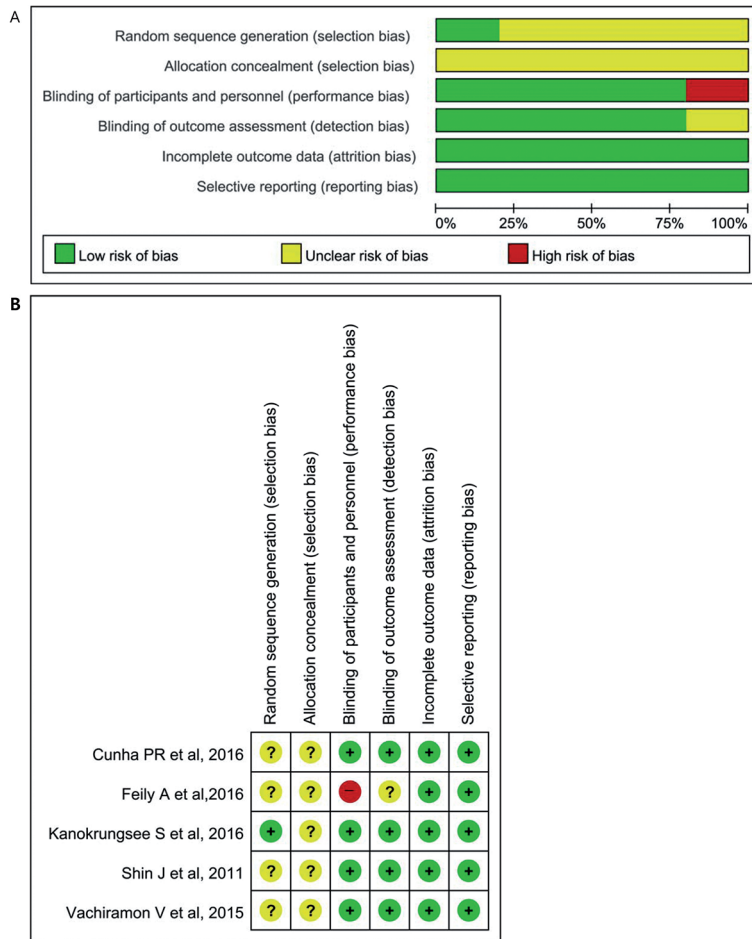


Fig S2. Risk of bias and methodological quality were assessed. For randomized controlled trials (RCTs), Cochrane Collaboration's "risk of bias" tool was used. (A) Risk-of-bias graph; (B) risk-of-bias summary.

A

Study or Subgroup	Experimental		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	
1.1.1 >50% re-pigmentation(facial vitiligo)							
Kanokrungeesee S et al, 2016	6	12	6	12	52.8%	1.00	[0.45, 2.23]
Subtotal (95% CI)		12		12	52.8%	1.00	[0.45, 2.23]
Total events	6		6				
Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (P = 1.00)							
1.1.2 >50% re-pigmentation(refractory vitiligo)							
Cunha PR et al, 2016	2	4	0	4	13.8%	5.00	[0.31, 79.94]
Shin J et al, 2011	1	10	0	10	11.6%	3.00	[0.14, 65.90]
Vachirammon V et al, 2015	6	26	1	26	21.8%	6.00	[0.78, 46.42]
Subtotal (95% CI)		40		40	47.2%	4.90	[1.15, 20.93]
Total events	9		1				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.14, df = 2 (P = 0.93); I ² = 0% Test for overall effect: Z = 2.14 (P = 0.03)							
Total (95% CI)		52		52	100.0%	2.10	[0.67, 6.61]
Total events	15		7				
Heterogeneity: Tau ² = 0.48; Chi ² = 4.48, df = 3 (P = 0.21); I ² = 33% Test for overall effect: Z = 1.26 (P = 0.21) Test for subgroup differences: Chi ² = 3.52, df = 1 (P = 0.06), I ² = 71.6%							
Study or Subgroup	Experimental		Control		Weight	Mean Difference	
	Mean	SD	Mean	SD		IV, Random, 95% CI	
1.4.1 physician improvement score(facial vitiligo)							
Kanokrungeesee S et al, 2016	2.2	1.8	2.2	1.9	12	9.5%	0.00 [-1.48, 1.48]
Subtotal (95% CI)					12	9.5%	0.00 [-1.48, 1.48]
Heterogeneity: Not applicable Test for overall effect: Z = 0.00 (P = 1.00)							
1.4.2 physician improvement score(refractory vitiligo)							
Shin J et al, 2011	0.9	1.1	0.2	0.4	10	39.6%	0.70 [-0.03, 1.43]
Vachirammon V et al, 2015	1.4	1.4	0.5	0.9	26	50.9%	0.90 [0.26, 1.54]
Subtotal (95% CI)					36	90.5%	0.81 [0.33, 1.29]
Heterogeneity: Tau ² = 0.00; Chi ² = 0.16, df = 1 (P = 0.69); I ² = 0% Test for overall effect: Z = 3.32 (P = 0.0009)							
Total (95% CI)					48	100.0%	0.74 [0.28, 1.19]
Heterogeneity: Tau ² = 0.00; Chi ² = 1.21, df = 2 (P = 0.55); I ² = 0% Test for overall effect: Z = 3.16 (P = 0.002) Test for subgroup differences: Chi ² = 1.05, df = 1 (P = 0.31), I ² = 4.5%							
Study or Subgroup	Experimental		Control		Weight	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI	
1.2.1 <=25% re-pigmentation(facial vitiligo)							
Kanokrungeesee S et al, 2016	4	12	5	12	6.3%	0.80	[0.28, 2.27]
Subtotal (95% CI)		12		12	6.3%	0.80	[0.28, 2.27]
Total events	4		5				
Heterogeneity: Not applicable Test for overall effect: Z = 0.42 (P = 0.68)							
1.2.2 <=25% re-pigmentation(refractory vitiligo)							
Cunha PR et al, 2016	2	4	4	4	8.1%	0.56	[0.22, 1.40]
Shin J et al, 2011	7	10	10	10	38.4%	0.71	[0.47, 1.09]
Vachirammon V et al, 2015	14	26	23	26	47.2%	0.61	[0.42, 0.89]
Subtotal (95% CI)		40		40	93.7%	0.64	[0.49, 0.85]
Total events	23		37				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.43, df = 2 (P = 0.81); I ² = 0% Test for overall effect: Z = 3.17 (P = 0.002)							
Total (95% CI)		52		52	100.0%	0.65	[0.50, 0.85]
Total events	27		42				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.57, df = 3 (P = 0.90); I ² = 0% Test for overall effect: Z = 3.17 (P = 0.002) Test for subgroup differences: Chi ² = 0.15, df = 1 (P = 0.69), I ² = 0%							
Study or Subgroup	Experimental		Control		Weight	Mean Difference	
	Mean	SD	Mean	SD		IV, Random, 95% CI	
1.5.1 Patients' overall satisfaction(facial vitiligo)							
Kanokrungeesee S et al, 2016	8	2.8	7.7	2.5	12	17.2%	0.30 [-1.74, 2.34]
Subtotal (95% CI)					12	17.2%	0.30 [-1.74, 2.34]
Heterogeneity: Not applicable Test for overall effect: Z = 0.29 (P = 0.77)							
1.5.2 Patients' overall satisfaction(refractory vitiligo)							
Shin J et al, 2011	1.7	1.6	0.4	0.7	10	52.6%	1.30 [0.22, 2.38]
Vachirammon V et al, 2015	5.7	2.9	3.5	2.6	26	30.2%	2.20 [0.70, 3.70]
Subtotal (95% CI)					36	82.8%	1.61 [0.73, 2.49]
Heterogeneity: Tau ² = 0.00; Chi ² = 0.91, df = 1 (P = 0.34); I ² = 0% Test for overall effect: Z = 3.60 (P = 0.0003)							
Total (95% CI)					50	100.0%	1.40 [0.53, 2.27]
Heterogeneity: Tau ² = 0.07; Chi ² = 2.25, df = 2 (P = 0.32); I ² = 11% Test for overall effect: Z = 3.15 (P = 0.002) Test for subgroup differences: Chi ² = 1.34, df = 1 (P = 0.25), I ² = 25.2%							

Fig S3. Efficacy of fractional carbon dioxide (CO₂) laser add-on to vitiligo. (A) Treatment success greater than 50% re-pigmentation rate, (B) physician improvement score, (C) re-pigmentation rate 25% or less, (D) patient's overall satisfaction. [Control] represents conventional treatment alone; [Experimental] denotes fractional CO₂ laser add-on to conventional therapy. CI: confidence interval.

Table SI. Characteristics of studies included in this review

Study, year, Country (ref)	Study design	Vitiligo subtype	Participant number, mean age, years (age range)	Mean disease duration, years (range)	Treatment measures	Treatment protocol			
						Type	Frequency	Duration	Assessment
Cunha et al., 2016, Brazil (6)	RCT, SB, WP	Symmetrical, stable, refractory vitiligo on the hands	4 adults, 32.3±11.4 (21-47), III-V	8.5±6.6 (1-15)	CO ₂ fractional laser Topical steroid Topical salicylic acid	10,600 nm fractional CO ₂ laser (PIXEL CO ₂ , Alma lasers) 0.05% betamethasone solution (ND), Salicylic acid solution (2%, Mantecorp Chemical and Pharmaceutical Industry, Brazil)	5 sessions of treatment, with an interval of 4 weeks Once a day, daily at night	5 months	ND
Felly et al., 2016, Iran (8)	RCT, SB, WP	Stable, refractory vitiligo	20 adults, 30.6±11.1, IV	11.9±6.6	CO ₂ fractional laser Autologous hair transplantation	10,600 nm fractional CO ₂ laser (MX-7000, Daeshin Enterprise Corporation, Seoul, Korea) Follicular grafts harvested from the scalp and transplanted in 1-cm grid pattern using a 1-mm punch	1 session of treatment Once, 5 days after fractional CO ₂ laser	3 months + 10 days	3 months after CO ₂ fractional laser
Helou et al., 2014, Lebanon (7)	Non-RCT*, SB, WP	Stable, refractory vitiligo	10 adults, 27±6.6, (20-42), III-V	6.3±7.7 (2-25)	NB-UVB Topical steroid CO ₂ fractional laser Sun exposure	NB-UVB (Dermalight 1000, Dr Honle medizintechnik, GmbH, Germany) Clobetasol 45% solution 10,600 nm fractional CO ₂ laser (FX_Lumemis Inc., Santa Clara, CA) Between 15:00 h and 18:00 h	Twice a week, starting 5 days after hair transplant Twice daily 3 sessions of treatment, with an interval of 1 month 2 h daily, starting 5 days after each fractional CO ₂ laser	3 months	2 months after the final laser session.
Kanokrungeee et al., 2016, Thailand (5)	RCT, SB, WP	Symmetrical vitiligo on the face	14 adults, 53.7±13.8, (26-70), IV	3.6±3.1 (0.2-9)	CO ₂ fractional laser Targeted broadband UVB	10,600 nm eCO ₂ laser (Lutronic Corporation, Goyang, Korea) Targeted broadband UVB (DualLight™, TheraLight Inc., Carlsbad, CA, USA),	10 sessions of treatment with 2-week interval 10 sessions of treatment with 2-week interval	5 months	3 months after the last treatment
Shin et al., 2011, Korea (3)	RCT, SB, WP	Symmetrical, stable, refractory vitiligo	10 adults, 59.5±10.4, (37-74), IV	16.8±18.3 (2.5-58)	CO ₂ fractional laser NB-UVB	0.05% clobetasol propionate cream (ND) 10,600 nm eCO ₂ laser (Lutronic Corporation, Goyang, Korea) NB-UVB (UV 7001K; Waldman, Villingen - Schwenningen, Germany)	Twice daily 2 sessions at 2 months interval Twice a week, starting 5 days after each laser treatment.	4 months	2 months after the overall treatment
Vachiramon et al., 2015, Thailand (4)	RCT, SB, WP	Symmetrical, stable vitiligo on the hands	27 adults, 51.2±8.5, III-V	5.9±2.1	CO ₂ fractional laser NB-UVB Topical steroid	10,600 nm eCO ₂ laser (Lutronic Corporation, Goyang, Korea) NB-UVB (M-series, Bryan, OH), 0.05% clobetasol propionate cream (ND)	1 week interval for 10 consecutive weeks. Twice weekly for 20 sessions Twice daily	2.5 months	3 months after the final treatment

RCT: randomized controlled trial; SB: single-blind; WP: within-patient trial; ND: not determined; CO₂: carbon dioxide; NB-UVB: narrow-band ultraviolet B.
*Newcastle-Ottawa Scale: 5.

Table SII. Interventions and clinical outcomes in the studies included in this review

Study, year, Country (ref)	Enrolled patients	Completed patients	Intervention	Physician improvement score	Clinical outcomes, n						Side-effects/recur	
					> 75%	> 50% (PP)	≤ 25% (PP)	0% (PP)	≤ 25% (ITT)	(0%) (ITT)		
Cunha et al, 2016, Brazil (6)	T: 4 C: 4	T: 4 C: 4	T: CO ₂ fractional laser + 0.05% clobetasol propionate cream + 2% salicylic acid solution C: 0.05% clobetasol propionate cream + 2% salicylic acid solution	2.0±1.4 0.0±0.0	T: 1 C: 0	T: 2 C: 0	T: 2 C: 4	T: 0 C: 4	T: 2 C: 4	T: 0 C: 4	Very satisfied (0) Satisfied (4) Dissatisfied (0) Very satisfied (0) Satisfied (0) Dissatisfied (4) 6.8	Itchy skin in one patient Pain (1–2.5)
Felty et al, 2016, Iran (8)	T: 20 C: 20	T: 20 (15 women, 5 men) C: 20	T: CO ₂ fractional laser + Autologous hair transplantation + NB-UVB + Clobetasol 45% solution C: Autologous hair transplantation + NB-UVB + Clobetasol 45% solution	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	NA NA	6.8 5.4	All patients: transient grade 1 tenderness and erythema
Kanoknungsee et al, 2016, Thailand (5)	T: 14 C: 14	T: 12 (7 women, 5 men) C: 12	T: CO ₂ fractional laser + Targeted broadband UVB + 0.05% clobetasol propionate cream C: Targeted broadband NB-UVB + 0.05% clobetasol propionate cream	2.2±1.8 2.2±1.9	T: 4 C: 5	T: 6 C: 6	T: 4 C: 5	T: 4 C: 4	T: 4 C: 4	T: 4 C: 4	8.0±2.8 7.7±2.5	Median pain score: 4.5 (0–8) Transient erythema Median pain score: 0 (0–5)
Helou et al, 2014, Lebanon (7)	T: 10 C: 10	T: 10 (9 women, 1 man) C: 10	CO ₂ fractional laser + sun light Sun light	2.8±0.9 1.7±0.7	T: 2 C: 0	T: 7 C: 1	T: 1 C: 4	NA NA	T: 1 C: 4	NA NA	6.9±0.6 4.9±0.7	All patients: Transient pain, burning sensation, erythema, edema
Shin et al, 2011, Korea (3)	T: 10 C: 10	T: 10 (7 women, 3 men) C: 10	T: CO ₂ fractional laser + NB-UVB C: NB-UVB	0.9±1.1 0.2±0.4	T: 0 C: 0	T: 1 C: 0	T: 7 C: 10	T: 5 C: 8	T: 7 C: 10	T: 5 C: 8	1.7±1.6 0.4±0.7	All patients: burning sense, erythema, post-laser crust
Vachiramon et al, 2015, Thailand (4)	T: 27 C: 27	T: 26 (15 women, 11 men) C: 26	T: CO ₂ fractional laser + NB-UVB + 0.05% clobetasol propionate cream C: NB-UVB + 0.05% clobetasol propionate cream	1.4±1.4 0.5±0.9	T: 2 C: 1	T: 6 C: 23	T: 14 C: 18	T: 11 C: 18	T: 11 C: 18	T: 11 C: 18	3.5±2.6	Pain score: 4.5±2.4 (25 of 26 lesions) Transient edema Tiny brown spots on the nail plate (few patients) Oozing and crusting (1 patient) Pain score: 1.1±2.1 9/12 of 26 lesions

Physician assessment: grade 0: no improvement; 1, 1–25%: minimal; 2, 26–50%: moderate; 3, 51–75%: good; and 4, >75%: excellent.
 Patient assessment: 10-point visual analogue scale (VAS, 0–10) and Very satisfied; satisfied; and dissatisfied.

Side effects: pain score (10-point visual analogue scales, 0–10).
 T: treatment; C: control; PP: per protocol; ITT: intention to treat; NA: not available; CO₂: carbon dioxide; NB-UVB: narrow-band ultraviolet B.