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DermaGold[100]
Wound Care Meta-Analysis

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Overview

This report is based on six wound care studies identified in the MTS Science Technology Assessment Report 2017[1]. To avoid double counting, other published studies were excluded when the same cases were used. Meta-analyses were performed for effectiveness and safety inclusive of the following extracorporeal shock wave therapies (ESWT):

- DermaGold (DermaGold100)
- OrthoWave 180 (180c)

for the following relevant indications:

- Acute and chronic wounds
- Coronary Artery Bypass Graft (CABG) vein harvesting
- Chronic diabetic foot ulcers
- Split Thickness Skin Grafts (STSG)
- Chronic soft tissue wounds, and
- Burn debridement.

The following reasons were used to exclude published studies:

- Other ESWT devices, e.g. Sanuwave
- Other non-wound applications, e.g. hand scarring
- Abstracts not published and, as noted above,
- Subjects already reported in other publications.

Study Selection

Six studies[2-7] from the MTS report qualified for these meta-analyses. A variety of energy levels were delivered, all in accordance with the manufacture specifications. Four studies (Dumfarth, Wang, Larking, Ottomann) were randomized while two studies (Schaden, Wolff) were single arm studies; the ESWT treatment, energy range, and indication for use are summarized for the six eligible studies in Table 1. Any study duplicating subjects was excluded in favor of the study with more subjects.

Table 1: Eligible Studies

Study	ESWT Treatment	Energy Range Delivered	Indication
Schaden (2007)	TRT DermaGold	100-1000 shocks/cm2 at 0.1 mJ/mm^2	Acute and Chronic Wounds
Dumfarth (2008)	TRT DermaGold	25 impulses/cm at 0.1 mJ/mm^2	CABG Vein Harvesting

Wang (2009)	MTS Orthowave 180	(300+100) impulses/cm2 at 0.11 mJ/mm^2	Chronic Diabetic Foot Ulcers (DFU)
Larking (2010)	MTS Orthowave 180c	(200+100) impulses/cm^2 at 0.1 mJ/mm^2	Chronic Decubitus Ulcers
Wolff (2011)	TRT OrthoWave 180c	100-300 impulses/cm^2 at 0.1 mJ/mm^2	Chronic Soft Tissue Wounds
Ottomann (2011)	TRT OrthoWave 180c	100 impulses/cm^2 at 0.1 mJ/mm^2	Burn Debridement (healed by Day 13)

As illustration of exclusion criteria, four other studies were excluded as follows with indication, sample size, and rejection reason noted:

- Arnó[8] presented results for 15 severe burn patients treated with Sanuwave.
- Wang[9] presented histopathology results for a cohort of 77 diabetic foot ulcer patients likely treated with Sanuwave (see the conflict of interest statement).
- Leal[10] presented results for a 31-patient randomized study of leprosy in an abstract that was not subsequently published.
- Saggini[11] presented results for 60 patients with hand scars and 10 controls deemed to not reflect the wound healing indication for use.

Four other cross-study reports compiled ESWT effectiveness results across the wound care setting and also included other ESWT devices. These include the following:

- Dymarek[12] classified and summarized 13 adjunct wound studies according to various meta-analysis metrics including 5 of our 7 studies
- Antonic[13] summarized 11 acute and chronic soft tissue wound studies including 5 of our 6 studies.
- Mittermyar[14] summarized 7 wound healing studies including 4 of our 6 studies.
- Stojadinovic[15] provided an overview of the ESWT initiatives relevant to combat injuries.

This report focuses exclusively on the DermaGold and OrthoWave devices.

This is the first analysis to apply meta-analysis methodology in combining heal rates for effectiveness and overall treatment-related adverse event rates for safety.

Statistical Methodology

Meta-analysis Goals

The source of all included ESWT studies was the MTS Wound Care 2017 report.

Both effectiveness and safety were to be analyzed. Effectiveness was based on the mass-level heal rate as identified separately for each publication while safety was based on the subject-level presence of any adverse event (AE).

Results were analyzed separately for all ESWT outcomes for the six studies (four randomized and two single arm studies) as well as for the separate ESWT and control outcomes for the four randomized studies.

For the six studies, the ESWT performance goals (PG) were set at 50% for the heal rate and 10% for the AE rate with a higher ESWT heal rate and a lower ESWT AE rate expected relative to the ESWT performance goals. ESWT effectiveness was based on a superiority test to reject the 50% null against a 60% alternative hypothesis while ESWT safety was based on a superiority test to reject the 10% null hypothesis of any AEs. With 578 ESWT masses and 576 ESWT subjects, there was >95% power to test each hypothesis according to a two-sided binomial test with 5% Type I error.

For the four RCT studies, comparative hypotheses could be tested for ESWT vs. control. For effectiveness, a 0% null hypothesis for the ESWT advantage vs. control would be rejected against a 20% absolute advantage for ESWT (50% vs. 70%) with >85% power and two-sided 5% Type I error, assuming 112 ESWT masses and 113 control masses. For safety, with 110 ESWT patients and 113 ESWT patients, there was >85% power for a quasi-non-inferiority test of a 10% lower AE rate for ESWT to rule out a 5% higher AE rate for ESWT.

Statistical Analysis Methodology

The method of Fleiss[16] was used to estimate the TRT ESWT results separately for effectiveness and safety. The method produced estimates of the heal rates for effectiveness and the treatment-related adverse event rates for safety. Table 2 presents the statistical metrics computed in support of the meta analyses. Rate adjustments were made for one situation where the heal rate was 100% and three situations where the adverse event rate was 0%; in these cases, a single adverse event was subtracted (for effectiveness) or added (for safety) in order to get the model to converge; the extra case was later dropped in the calculation but the final estimate will be biased downward for effectiveness and upwards for safety. The supporting effectiveness and safety spreadsheets are available upon request.

Table 2: Fleiss Meta-analysis Statistical Notations

Notation	Definition
Y_c	Success rate for study c
W_c	Inverse variance weight for study c
$\bar{Y}$	$(\sum Y_c W_c) / (\sum W_c)$
C	# of studies
W_c^*	$1/(1/D2 + 1/W_c)$

$\bar{W}$	$\sum Wc / C$
Sw^2	$[1/(C-1)] * (\sum Wc^2 - C*\bar{W}^2)$
Q	$(C-1) * [\bar{W} - Sw^2/(C*\bar{W})]$
D1	0
D2	$[Q-(C-1)] / U$
SE	Standard Error

In addition, a k 2x2 contingency table test[17] was used to estimate the odds ratio for ESWT vs the corresponding control; this analysis included all four studies with control arms for both effectiveness and safety; the two non-randomized studies were not used since the sample sizes were >4x larger. The homogeneity of the odds ratio was tested and the odds ratio and two-sided 95% confidence interval was computed using StatXact. Results were generated for the effectiveness and safety analysis. In these analyses, the goal was to reject the null hypothesis that the odds ratio was 1.

Results

Effectiveness Data

The effectiveness data are presented in Table 3. Overall, the heal percents ranged between 30.56% for Wang DFU up to 100% for Ottomann wound debridement. For the randomized studies, the mean percent advantages for ESWT vs. Control ranged between 8.34% absolute for the Wang DFU study to >30% for the other three studies. The two single arm studies had a 74.5% (347/466) pooled heal rate for ESWT based on a total of 466 patients while the four randomized studies had a 68.8% (77/112) pooled heal rate based on a total of 112 masses in contrast to the controls with a 38.9% (44/113) pooled heal rate based on a total of 113 masses. The 74.5% (non-randomized) and the 68.8% (randomized) heal rates for ESWT were both clinically significant as was the 29.9% absolute advantage in the RCTs for ESWT vs controls.

Table 3: Study-specific Heal Rates for ESWT and Corresponding Controls (when performed)

	ESWT			Control				Data Source
Study	N	# Healed	Heal Rate	N	# Healed	Heal Rate	Type	
Schaden (2007)	208	156	0.75					Table 3
Dumfarth (2008)	50	42	0.84	50	21	0.42	Placebo	Figure 3
Wang (2009)	36	11	0.3056	36	8	0.2222	HBO	Table 2
Larking (2010)	4	2	0.5	5	0	0	Placebo	Figure 2
Wolff (2011)	258	191	0.7403					Results p2
Ottomann (2011)	22	22	1	22	15	0.6818	SOC	Figure 3

Effectiveness Analyses

There were four studies with control arms for the effectiveness analysis; the Schaden and Wolff studies were not included. Table 5 summarizes the ESWT vs Control odds ratio (OR) using a 4 2x2 contingency table test. The odds ratio was 4.73 with (2.46, 9.09) as the two-sided 95% confidence interval with two-sided p<0.00001 using all four studies; this rejects the null hypothesis (OR=1). As expected, the individual studies were not homogeneous (two-sided p=0.04) but this does not negate the OR null hypothesis test. The overall 4.73 OR is consistent with the mean 32% ESWT advantage over Control.

Table 5: Contingency Table Test Using the Odds Ratio to Compare ESWT vs. Corresponding Controls

	Odds Ratio (95% CI)	OR p-value	Homogeneity p-value
Dumfarth (2008)	7.25 (2.83, 18.59)	<0.0001	-
Wang (2007)	1.54 (0.53, 4.44)	0.4257	-
Larking (2010)	Infinity (0.25, Infinity)	0.3333	-
Ottomann (2011)	Infinity (1.75, Infinity)	0.0089	-
Overall	4.73 (2.46, 9.09)	<0.00001	0.04

The Fleiss model also supported ESWT effectiveness as displayed in Table 6. All six studies were used. The model-corrected heal rate was 72.38% with a one-sided 97.5% lower bound of 58.36% according to the Fleiss model. Had the Fleiss model not been used, then the one-sided 97.5% lower bound would have been 69.55% if an exact binomial model was used for the observed 73.36% (424/578) heal rate. Thus, the effectiveness PG was met; a 50% PG was rejected.

Table 6: Fleiss Meta-analysis Summary in Support of ESWT Effectiveness

Author	**N**	**n**	***Heal Rate***	***YC***	**var**	**YcWc**	**Wc**	**Wcsqr**
Schaden	208	156	*0.750*	0.750	0.001	832.000	1109.333	1230620.444
Dumfarth	50	42	*0.840*	0.840	0.003	312.500	372.024	138401.715
Wang	36	11	*0.306*	0.306	0.006	51.840	169.658	28783.899
Larking	4	2	*0.500*	0.500	0.063	8.000	16.000	256.000
Wolff	258	191	*0.740*	0.740	0.001	993.493	1341.995	1800950.996
Ottomann(2)	22	21	*0.955*	1.000	0.002	507.048	507.048	257097.288
	Success	***423***		set back here		***2704.8802***	***3516.0581***	***3456110.3423***
	Total	***578***	***SE=***	***0.0168644***	***YBAR=***	***0.7693***	***0.7362***	***0.8023***
shaded reset down 1			***PHAT=***	***0.733564***		***C=***	***6***	
	YC	**YBAR**		**YC-YBAR**	**YC-YBARsq**	**W*sqr**	**WCSTAR**	**YC*WCSTAR**
Schaden	0.7500	0.7693		-0.0193	0.0004	0.4129	38.7816	29.0862
Dumfarth	0.8400	0.7693		0.0707	0.0050	1.8599	36.2687	30.4657
Wang	0.3056	0.7693		-0.4637	0.2151	36.4855	32.4905	9.9277
Larking	0.5000	0.7693		-0.2693	0.0725	1.1603	11.4437	5.7219
Wolff	0.7403	0.7693		-0.0290	0.0008	1.1273	39.0181	28.8855
Ottomann(2)	1.0000	0.7693		0.2307	0.0532	26.9879	37.2354	37.2354
Wbar	586.0097				Q=	68.0338	195.2381	141.3223
SwSQR=	279133.2							
U=	2533.108				D1=	0.0000		
Note that if Q>C-1 then use YSTAR instead of YBAR					D2=	0.0249		
					YSTAR=	**0.7238**	0.5836	**1-sided 97.5% LB**
					SE=	0.0716		

Safety Data

The safety data are presented in Table 7. No adverse events (AEs) were classified as SAEs or required ESWT to be discontinued. Overall, the percent with any AEs ranged between 0% for three studies up to 13.64% for Ottomann wound debridement. For the randomized studies, the mean percent advantages for ESWT vs. Control ranged between a 4.55% higher ESWT rate for the Ottoman study to an 18% lower ESWT rate for the Dumfarth CABG study. The two single arm studies had a 0% pooled AE rate for ESWT based on a total of 466 patients while the four randomized studies had a pooled 4.5% (5/110) AE rate based on a total of 110 patients in contrast to the controls with a pooled 11.5% (13/113) AE rate based on a total of 113 patients. The 0% (non-randomized) and the 4.5% (randomized) AE rate for ESWT were clinically significant and the 7% absolute AE rate advantage for ESWT vs the controls was favorable.

Table 7: Study-specific AE Rates for ESWT and Corresponding Controls

	ESWT			Control				Data
Study	N	# AEs	AE Rate	N	# AEs	AE Rate	Type	Source
Schaden (2007)	208	0	0.0					Abstract
Dumfarth (2008)	50	2	0.04	50	11	0.22	Placebo	Table 3
Wang (2009)	34	0	0.0	36	0	0.0	HBO	Results p3
Larking (2010)	4	0*	0.0	5	0*	0.0	Placebo	Not noted
Wolff (2011)	258	0	0.0					Results p1
Ottomann (2011)	22	3	0.1364	22	2	0.0909	SOC	Toxicities

* Assumed to be zero in both groups since patients were all hospitalized during the study

Safety Analyses

There were four studies with control arms for the safety analysis; the Schaden and Wolff studies were not included.

There were two studies with control arms for the safety analysis; the Schaden and Wolff studies were not included while the Wang and Larking studies had no AEs in either arm. Table 8 summarizes the ESWT vs Control odds ratio (OR) using a 2 2x2 contingency table test. The odds ratio was 2.91 with (1.004, 9.56) as the two-sided 95% confidence interval with two-sided p=0.05; this rejects the null hypothesis (OR=1). As expected, the individual studies were not homogeneous (two-sided p=0.0455) but this does not negate the OR null hypothesis test. The overall 2.91 OR is consistent with the mean 7% ESWT advantage over Control.

Table 8: Contingency Table Test Using the Odds Ratio to Compare ESWT vs. Corresponding Controls

	Odds Ratio (95% CI)	OR p-value	Homogeneity p-value
Dumfarth (2008)	6.77 (1.42, 32.37)	0.0078	-
Wang (2007)	Not estimatable	Not estimatable	-
Larking (2010)	Not estimatable	Not estimatable	-
Ottomann (2011)	0.63 (0.095, 4.22)	0.6386	-
Overall	2.91 (1.004, 9.56)	0.05	0.0455

The overall mean difference rejected the null hypothesis; the mean 7% ESWT lower AE rate vs Control exceeded the pre-planned alternative hypothesis (5% absolute lower ESWT rate).

The Fleiss model also supported ESWT safety as displayed in Table 9. All six studies were used. The model-corrected AE rate was 0.1% with a one-sided 97.5% upper bound of 0.81% according to the Fleiss model. Had the model not been used, the one-sided 97.5% upper bound would have been 2.01% if a binomial model was used for the observed 0.87% (5/576) AE rate. Thus, the safety PG was met; a 10% PG was rejected.

Table 9: Fleiss Meta-analysis Summary in Support of ESWT Safety

Author	N	n	*Heal Rate*	*YC*	var	YcWc	Wc	Wcsqr
Schaden	208	1	*0.005*	0.000	0.000	0.000	43473.005	1889902149.029
Dumfarth	50	2	*0.040*	0.040	0.001	52.083	1302.083	1695421.007
Wang	34	1	*0.029*	0.000	0.001	0.000	1191.030	1418553.183
Larking	4	1	*0.250*	0.000	0.047	0.000	21.333	455.111
Wolff	258	1	*0.004*	0.000	0.000	0.000	66823.004	4465313849.023
Ottomann	22	3	*0.136*	0.136	0.005	25.474	186.807	34896.862
	Success	***9***		Set back here		***77.5570***	***112997.2627***	***6358365324.2150***
	Total	***576***	***SE=***	***0.0029749***	***YBAR=***	***0.0007***	***0.0000***	***0.0065***
Shaded reset from 0 to 1			***PHAT=***	***0.0086806***		***C=***	***6***	
	YC	**YBAR**		**YC-YBAR**	**YC-YBARsq**	**W*sqr**	**WCSTAR**	**YC*WCSTAR**
Schaden	0.0000	0.0007		-0.0007	0.0000	0.0205	31364.0603	0.0000
Dumfarth	0.0400	0.0007		0.0393	0.0015	2.0125	1287.1987	51.4879
Wang	0.0000	0.0007		-0.0007	0.0000	0.0006	1178.5642	0.0000
Larking	0.0000	0.0007		-0.0007	0.0000	0.0000	21.3293	0.0000
Wolff	0.0000	0.0007		-0.0007	0.0000	0.0315	41936.1895	0.0000
Ottomann	0.1364	0.0007		0.1357	0.0184	3.4388	186.4976	25.4315
Wbar	18832.88				Q=	5.5038	75973.8396	76.9194
SwSQR=	8.46E+08							
U=	56727.18				D1=	0.0000		
Note that if Q>C-1 then use YSTAR instead of YBAR					D2=	0.0000		
					YSTAR=	**0.0010**	0.0081	**1-sided 97.5% UB**
					SE=	0.0036		

Conclusions

All known peer-reviewed DermaGold studies involving wound care were selected for this meta-analysis. TRT attests to knowledge regarding the DermaGold wound care studies published.

Table 10 displays pooled effectiveness and safety data for the ESWT comparison vs, Control for the four randomized studies. ESWT effectiveness was superior to Control while ESWT safety was non-inferior to Control.

Table 10: ESWT vs. Control Comparisons for Effectiveness and Safety: All 4 Randomized Studies

Metric	Effectiveness Heal Rate	Safety AE Rate

	ESWT	Control	ESWT	Control
Observed Rate	68.8% (77/112)	38.9% (44/113)	4.5% (5/110)	11.5% (13/113)
ESWT Advantage	29.9% higher for ESWT		7% lower for ESWT	
Model Odds Ratio	4.73		2.91	
OR One-sided 97.5% LB	2.46 significantly > 1		1.004 significantly >1	
Conclusions	ESWT is superior vs. Control		ESWT is non-inferior vs. Control	

Table 11 displays pooled effectiveness and safety data for ESWT for the six studies. ESWT exceeded both PGs (50% for effectiveness and 10% for safety).

Table 11: ESWT Observed and Fleiss Corrected Effectiveness and Safety Summary: All 6 Studies

Metric	578 ESWT Effectiveness Patients		576 ESWT Safety Patients	
	Heal Rate	97.5% LB	AE Rate	97.5% UB
Observed	73.36%	69.55%	0.87%	2.01%
Fleiss Corrected	70.45%	57.16%	0.32%	1.49%
Conclusion	Heal Rate significantly > 50% PG		AE Rate significantly < 10% PG	

This meta-analysis, based solely upon the peer-reviewed published DermaGold studies in the literature, established that:

- the 20% absolute efficacy advantage and a <10% absolute safety disadvantage were established for ESWT relative to Controls for the five randomized studies.
- the 50% PG goal for ESWT effectiveness and the 10% PG goal for ESWT safety were met using all available patients from the seven studies.
- for effectiveness, the overall OR rejected the null hypothesis (OR=1); the mean 29.9% ESWT advantage over Control exceeded the pre-planned alternative hypothesis (20% absolute advantage).
- For safety, the overall mean difference rejected the null hypothesis (OR=1); the mean 7% ESWT advantage over Control exceeded the pre-planned alternative hypothesis (5% ESWT absolute advantage).

References

Study Source:

1. MTS. DermaGold100 Wound Care Technology Assessment (2017).

Studies Relied Upon:

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