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Pilot Study of a Topical Adhesive Containing Anesthetic and Heating Components to Reduce Injection Pain with Subcutaneous Multiple Sclerosis Medications

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Background

- Pain and other local injection site reactions (ISR), including pruritis and erythema, are common with injectable multiple sclerosis (MS) medications.[i]
- ISR are responsible for non-adherence, poor sleep, anxiety, needle phobia and depression and are among the most common reasons for discontinuation of therapy for interferon beta (IFN) and the most common reason for discontinuation of glatiramer acetate (GA).[ii]
- Relieving injection site pain may improve the tolerability of MS medications.
- SYNERA™ is a peel-and-stick topical adhesive (S-TA) with a novel heating component designed to enhance the delivery of an anesthetic mixture of lidocaine 70mg and tetracaine 70mg.[iii] S-TA has a controlled heat-assisted drug delivery (CHADD) system to warm the skin and facilitate drug delivery. This adhesive is approved in the USA for use in dermal analgesia for superficial venous access and superficial dermatological procedures and may be useful in reducing MS drug injection pain and needle phobia.
- This was the first study to assess the effect of S-TA on pain with injectable subcutaneous IFN and GA in MS.

Figure 1. S-TA adhesive

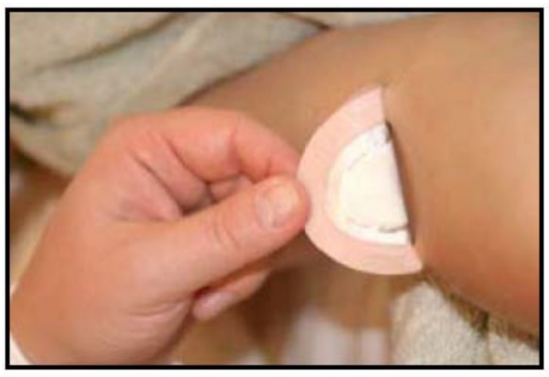
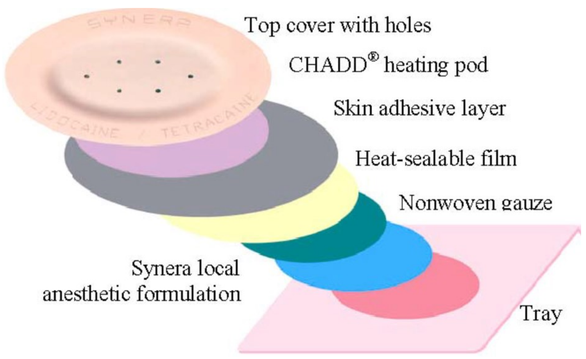


Figure 2. S-TA adhesive composition



Objective

To assess the effect of S-TA on immediate pain and other measures of discomfort with SC MS drug injection and to determine the preferred period of application (30 vs. 60 minutes) prior to injection.

Methods

- This was an open-label, uncontrolled trial with pre- and post-testing of one MS cohort with two active periods: S-TA application for 60 minutes before each injection and S-TA application for 30 minutes before each injection. S-TA was to be removed immediately before injection. (**Figure 3**)
- The duration of each treatment period was determined by the patient's injectable medication [see Figure 3, varying from 2 weeks (GA 20mg) to 4 weeks (IFN and GA 40mg)].
- Diaries were used to record most outcome measures at home.
- 30 patients meeting all eligibility criteria (**Table 1**) were enrolled.
- The primary efficacy measure was the change in mean pain on injection [0-10 visual analogue scale (VAS)] relative to baseline.
- Secondary efficacy measures included the following patient-reported outcomes, which were all performed at baseline and end of both study periods:
  - Pain at 12-hrs post injection (0-10 VAS)
  - Pain at 24-hrs post injection (0-10 VAS)
  - Fear of injection (0-10 VAS, recorded immediately before each injection)
  - Local Injection Site Reaction (LISR) scale (0-6, 0 = no reaction, see ref.[iv])
  - Injection site tenderness (0-10 VAS)
  - Global Impression (level of "comfort" with injections over past two weeks, 1-7 VAS, 1= extremely bad, 7= extremely good)
- Statistical analyses were performed using Student's t test (Pr > | t |) for parametric and Signed Rank (PR >= |S|) for non-parametric results. Null Hypothesis: Change mean or median = 0.

Figure 3. Study Design

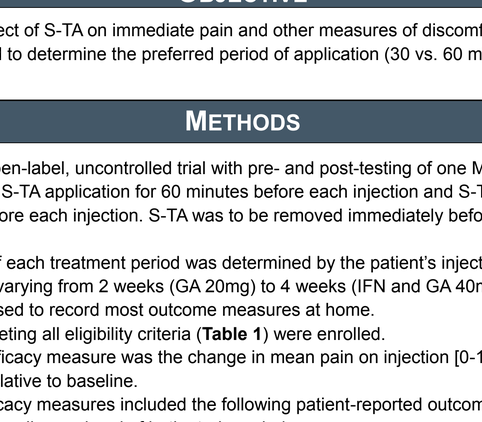


Table 1. Eligibility Criteria

Inclusion Criteria

- Confirmed diagnosis of MS based on McDonald or Poser criteria (no sub-type restrictions).
- Aged >18.
- Regular use of interferon beta subcutaneous or glatiramer acetate subcutaneous.
- No change in disease modifying therapy in 60 days.
- Mean score of ≥1.0 on Local Injection Site Reaction scale and Mean Pain Upon Injection score of ≥3.0 during baseline period.
- No MS exacerbation for 60 days prior to screening.
- Written informed consent.

Exclusion Criteria

- Females who are breast-feeding, pregnant.
- Severe cognitive deficits.
- Concurrent application of any topical medication to treat injection site reactions.
- History of allergy to lidocaine, tetracaine or PABA (para-amino benzoic acid) containing products.
- Patients receiving class 1 antiarrhythmic agents (i.e. tocainide, mexilitine).
- Any other serious and/or unstable medical condition.

Results

- There were 7 screen failures, (Low pain level = 5, withdrew consent = 1, no diary = 1).
- A total of 30 patients were enrolled. There was 1 early termination (on GA 20mg).
- Twenty-nine patients completed (GA =25, IFN =4). See Table 2.

Table 2. Demographics and Baseline Disease Characteristics

		Completed Patients		
		Copaxone (N=25)	Interferon (N=4)	Total (N=29)
Age (years)	Mean ± SD	52.4 ± 9.63	42.8 ± 10.6	51.0 ± 10.1
Gender	F	23 (92.0%)	2 (50.0%)	25 (86.2%)
	M	2 (8.0%)	2 (50.0%)	4 (13.8%)
Race	African American	1 (4.0%)	0 (0.0%)	1 (3.4%)
	Caucasian	23 (92.0%)	4 (100.0%)	27 (93.1%)
	Hispanic	1 (4.0%)	0 (0.0%)	1 (3.4%)
Duration of disease (years)	Mean ± SD	14.8 ± 8.92	12.5 ± 6.61	14.5 ± 8.57
MS type	PPMS	1 (4.0%)	0 (0.0%)	1 (3.4%)
	RRMS	19 (76.0%)	4 (100.0%)	23 (79.3%)
	SPMS	5 (20.0%)	0 (0.0%)	5 (17.2%)
Screening EDSS	Mean ± SD	4.04 ± 2.03	2.25 ± 1.26	3.79 ± 2.02

Table 3. Injection Related Patient Reported Outcomes

			Completed Patients		
			Copaxone (N=25)	Interferon (N=4)	Total (N=29)
Fear of Injection	Baseline	Mean ± SD	3.82 ± 2.69	4.09 ± 1.27	3.86 ± 2.52
	S-TA 60 minutes	Mean ± SD	2.54 ± 2.31	3.52 ± 2.56	2.68 ± 2.32
	S-TA 30 minutes	Mean ± SD	2.17 ± 2.24	2.34 ± .681	2.19 ± 2.09
Pain on Injection	Baseline	Mean ± SD	5.69 ± 1.64	5.77 ± 1.84	5.70 ± 1.63
	S-TA 60 minutes	Mean ± SD	3.20 ± 1.96	2.78 ± 2.26	3.14 ± 1.97
	S-TA 30 minutes	Mean ± SD	3.25 ± 1.87	1.81 ± .558	3.05 ± 1.82
Pain after 12 HR	Baseline	Mean ± SD	3.20 ± 1.82	1.53 ± .729	2.97 ± 1.80
	S-TA 60 minutes	Mean ± SD	1.88 ± 1.51	.765 ± 1.02	1.72 ± 1.49
	S-TA 30 minutes	Mean ± SD	2.01 ± 1.52	.378 ± .516	1.78 ± 1.53
Pain at 24 HR	Baseline	Mean ± SD	2.43 ± 1.77	1.03 ± .967	2.24 ± 1.74
	S-TA 60 minutes	Mean ± SD	1.49 ± 1.55	.833 ± 1.01	1.39 ± 1.49
	S-TA 30 minutes	Mean ± SD	1.38 ± 1.25	.285 ± .570	1.23 ± 1.23
Tenderness at 24 HR	Baseline	Mean ± SD	3.12 ± 1.87	2.70 ± 3.04	3.06 ± 2.00
	S-TA 60 minutes	Mean ± SD	2.00 ± 1.39	1.69 ± 1.81	1.96 ± 1.42
	S-TA 30 minutes	Mean ± SD	1.88 ± 1.16	.985 ± 1.17	1.76 ± 1.18
Local Injection Site Reaction Score	Baseline	Mean ± SD	3.09 ± 1.50	2.15 ± 1.01	2.96 ± 1.47
	S-TA 60 minutes	Mean ± SD	2.18 ± 1.44	1.22 ± .728	2.04 ± 1.40
	S-TA 30 minutes	Mean ± SD	2.13 ± 1.33	.873 ± .941	1.95 ± 1.35

Primary and Key Secondary Outcome Measures

All results are for GA and IFN patients, combined, N = 29.

Figure 4. Primary outcome: Pain on injection (immediate pain)

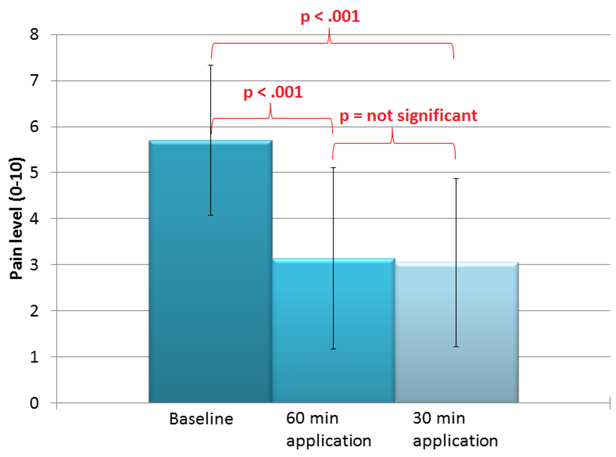


Figure 5. Pain at 12-hours post-injection

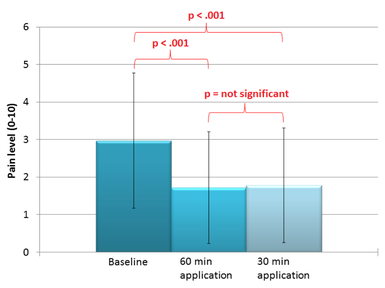


Figure 6. Pain at 24-hours post-injection

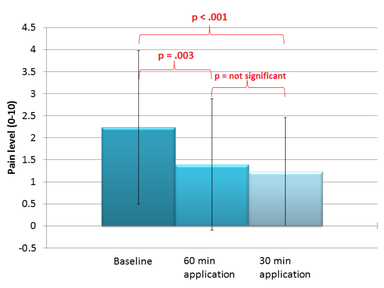


Figure 7. Fear of Injection (0-10 VAS, recorded immediately before each injection)

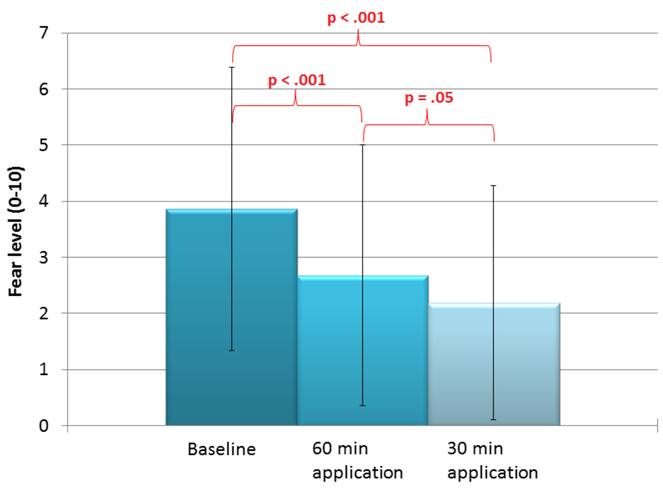


Figure 8. Tenderness Rating at 24-hours post-injection

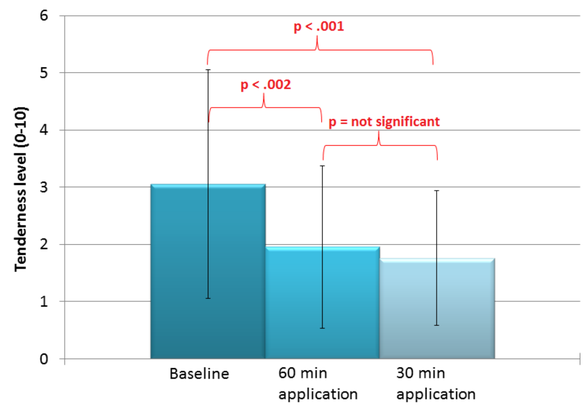


Figure 9. Local Injection Site Reaction scale (0-6) at 24-hours post-injection

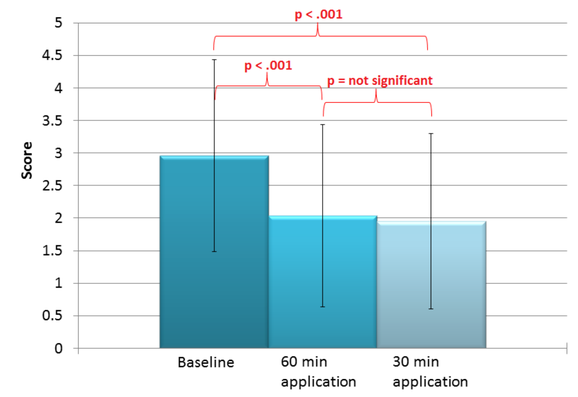
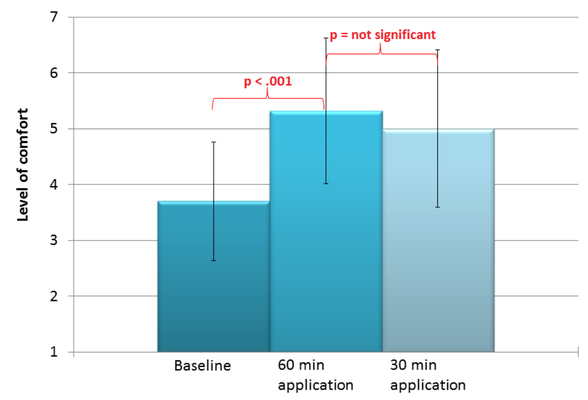


Figure 10. Global Impression (level of "comfort" with injections, 1-7 scale)



Adverse Events (AE)

Two treatment related adverse events were recorded: allergic reaction involving muscle spasm and lightheadedness (N=1, moderate AE, subject on GA, withdrew) and dermatitis (N=1, mild AE, subject on GA, completed).

Discussion

Significant reductions in pain of injection were found with both 30-minute and 60-minute applications of S-TA. The difference between the two applications was not significant.

Significant reductions in pain at 12 hours, pain at 24 hours, tenderness at 24 hours and Local Injection Site Reaction (LISR) scale score (at 24 HR) were found with both 30-minute and 60-minute applications of S-TA.

There were no significant differences between 30-minute and 60-minute applications for these outcomes.

Fear of injection (FOI) was significantly reduced with both S-TA 30-minute and 60-minute applications. FOI was significantly less with S-TA for 30-minutes than for 60-minutes, possibly related to a period effect.

Global Impression of level of comfort with injections was best for ST-A 60-minute application. The difference was significant vs. baseline ($p < 0.001$), but not vs. S-TA 30-minute application ($p = 0.1$).

Subgroup analysis showed very similar results for GA group (N=25) and number was insufficient (N=4) for IFN group.

Limitations

This was an uncontrolled, open-label trial. Subject numbers were small, especially for patients on interferon. Period effects cannot be excluded.

Conclusions

This pilot study explored the clinical utility of a topical adhesive (S-TA) containing anesthetic and heating components in managing subcutaneous medication injections used for MS treatment.

S-TA applied for 30 or 60 minutes prior to subcutaneous drug injection significantly reduced pain on injection, pain at 12 hours, pain, tenderness and LISR at 24 hours, and fear of injection. Pain reductions were similar with 60-minute and 30-minute application of S-TA, suggesting that the shorter application time may be adequate.

Our findings support further study to establish the utility of this novel approach to treat injection pain caused by subcutaneous MS drug injections.

References

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Acknowledgements

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