Open-label, randomised, multicentre crossover trial assessing two-layer compression bandaging for chronic venous insufficiency: results of the APRICOT trial

Abstract

Compression bandaging is the mainstay therapy for chronic venous insufficiency and venous leg ulcers, but patient compliance can be challenging due to associated discomfort. The study discussed here aimed to compare AndoFlex TLC Calamine and Coban2 compression bandaging in relation to patient comfort and pruritus symptomology, with severity of pruritus as the primary outcome. This was a multi-centre, prospective, non-blinded, randomised controlled crossover trial involving 39 randomised patients with chronic venous insufficiency patients. In two periods, the patients wore AndoFlex TLC Calamine or Coban2 for 3 weeks each. No significant differences in validated pruritus outcome measures were observed, including a non-significant treatment effect for the severity of pruritus scale (n=35 trial completers; p-value=0.24, Wilcoxon test). However, after trying both bandages, 21 of the 35 patients (60%) definitely preferred AndoFlex TLC Calamine, whereas 4 patients (11%) definitely preferred Coban2. Thus, AndoFlex TLC Calamine compression bandage therapy was preferred by most patients, although this observation could not be confirmed using validated patient-reported outcome measures for pruritus. Further research is indicated to establish if patient preference translates into favourable clinical outcomes.

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■ Chronic venous insufficiency ■ Crossover trial ■ Pruritis ■ Compliance ■ Compression therapy

Leon Jonker, Jane Todhunter, Lesley Robinson, Stacey Fisher

Leon Jonker, Science and Innovation Manager, North Cumbria Integrated Care NHS Foundation Trust, Carlisle

leon.jonker@ncic.nhs.uk

Jane Todhunter, Specialist Vascular Nurse, North Cumbria Integrated Care NHS Trust

Lesley Robinson, Specialist Vascular Nurse, North Cumbria Integrated Care NHS Trust

Stacey Fisher, Research GP, North Cumbria Integrated Care NHS Trust

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Chronic venous insufficiency (CVI) is associated with a host of different conditions, ranging from varicose veins to venous leg ulcers (VLUs). It is well-established that the Western lifestyle associated with obesity and lack of exercise increases the risk of CVI; in the US, for example, CVI is the seventh leading cause of disability (Graves and Zheng, 2014). Similar high incidences are found in Europe, with the prevalence of varicose veins exceeding 10% among adults in Scotland (Bergan et al, 2006).VLUs are the most common type of leg ulcers, affecting 1–3% of the population over 60 years, and this incidence is expected to increase with the ageing population (Graham et al, 2003; Scottish Intercollegiate Guidelines Network, 2010). Each year, the NHS spends £2.3–£3.1bn (at 2005–2006 cost) on dressings and associated products, equating to 3% of the total estimated health expenditure (Posnett and Franks, 2008). Further, patients with wounds cost the NHS up to £5 billion more per annum than matched control patients (Guest et al, 2015).

The mainstay of treatment of VLUs is the reversal of venous hypertension through compression bandaging, to be followed by intervention to treat the venous reflux (O'Brien et al, 2012). However up to 15–30% cases do not respond to this gold-standard treatment and remain unhealed even after 6 months of treatment (Moffatt et al, 2006; O'Meara et al, 2009). Treatment success in CVI is highly dependent on achieving high levels of patient compliance. Unfortunately, compliance rates are often poor in this population (Heinen et al, 2007). Minimising the frequency of undesirable effects related to compression bandaging may make the therapy more acceptable. Apart from bandage slippage, the most common undesirable effects of wearing compression bandaging are skin-related: pruritus develops in as many as one in three patients and can be a reason for non-compliance in one in five patients (Reich-Schupke et al, 2009; Stansal et al, 2013; Ayala et al, 2019). Some decades ago, Unna's boot was developed, which comprised a gauze dressing impregnated with calamine, a compound substance composed primarily of zinc oxide and less than 1% ferric oxide (Rubin et al, 1990). Technology has advanced, and compression bandaging products tend to be two-layer short-stretch systems (Hanna et al, 2008).

Unna's boot has been shown to be effective at controlling pruritis in different conditions, including burns-related long-term itch (Shohrati et al, 2007). Recently, Andover Healthcare (part of Milliken & Company) introduced a two-layer short-stretch compression bandage that contains calamine, although its performance in relation to other existing compression bandage products has not been appraised (Todd, 2019). The aim of the present randomised, controlled, crossover trial was to determine patient experience and preference concerning two different two-layer compression bandaging systems, namely, Andover Healthcare's AndoFlex TLC Calamine and 3M's Coban2 system in a population of patients who required compression bandaging due to CVI. Severity of pruritus was the primary outcome.

Methods

Study design and patients

The APRICOT pilot study (A Patient and clinician Reported Impression of COmpression Therapy study) is a multi-centre, prospective, controlled crossover trial of two compression bandaging systems, involving patients deemed to benefit from this intervention. Patients were enrolled from four NHS organisations in England: one vascular department in a hospital trust and three GP practices. Full research governance clearance was obtained from the National Research Ethics Service (reference 18/WA/0383), Health Research Authority (reference 252438) and the NHS trusts; the study was also registered on the International Standardised Clinical Trial Number registry under reference ISRCTN95282887.

The crossover study design was opted to measure the degree of itchiness caused by either of the compression bandage systems in the same patient, and measure patient preference. The presence of pruritus was not a qualifying criterion for eligible patients. A washout or non-compression period was not feasible for this patient population, but the risk of carry-over effect was minimised by having a 3-week trial period per compression bandage brand and then administering questionnaires that covered a shorter period.

Eligibility criteria for the patients were mental capacity and command of English, age 18 years or older, a clinical diagnosis of CVI and a comprehensive classification system for chronic venous disorders (CEAP) clinical score of C2 or higher (Eklof et al, 2004). Exclusion criteria were limited life expectancy (i.e. those receiving palliative care); a history of not being able to tolerate compression, calamine or zinc oxide; and an ankle brachial pressure index (ABPI) of <0.5. Written informed consent was obtained, after which participants were allocated 1:1 at random to commence either Coban2 or AndoFlex®TLC Calamine therapy first, using a non-restricted randomised sequence generated for the entire sample using a freeware randomisation programme called Randomizer.org. Sequential envelopes with each next randomisation allocation were used to achieve concealment—there was no block randomisation by recruiting centre. A member of the study team who did not see patients generated the randomisation sequence, and clinical staff enrolled patients and assigned the participants to the interventions. Since the primary focus was symptomology and not wound healing, there was no prerequisite for patients to have an ulcer, and no stratification for ulcer size or chronicity was made. As the study involved compression bandages that looked different, it was not possible to achieve blinding for the participants, clinical or research staff.

Intervention and outcomes

At baseline (week 0), patients who either newly required or were already prescribed leg compression bandaging were allocated to wear one brand of compression bandage for 3 weeks first (pre-crossover, i.e. up to week 3), after which they wore the second brand for 3 weeks (post-crossover, i.e. up to week 6). The standard choice of compression bandage outside of the trial was Coban2. Patients receiving both 'Lite' (25–30 mmHg) and normal (35–40 mmHg) compression were invited to participate since they were administered the corresponding equivalent before and after crossover. Further Coban2 Lite and AndoFlex TLC Calamine Lite, plus Coban2 and AndoFlex TLC Calamine, respectively, offer comparable compression. For all patients, the standard practice of applying emollient (Epaderm or Dermol in this study) before applying compression bandaging continued, both before and after crossover (Brown and Butcher, 2005).

In weeks 0, 3 and 6, clinical and patient-related outcome measures were recorded. Pruritus was measured through patient feedback using the Severity of Pruritus Scale (SPS) score (Yosipovitch et al, 2017), visual pruritus score (Reich et al, 2012) and the 5-D itch score (Elman et al, 2010). Wound size was determined using the pressure ulcer scale for healing (PUSH) score tool, which is also validated for use on VLUs (Ratliff and Rodeheaver, 2005). Patient-reported quality of life in relation to their vascular disease was measured using the chronic venous disease quality of life questionnaire (CIVIQ-20) (Launois et al, 2010). The venous clinical severity score (VCSS)

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was used by the clinical staff to report on status of the venous insufficiency and related symptomology (Vasquez et al, 2010). Further, patient feedback recorded included that on bandage comfort over the 3 weeks that it had been worn (including a survey list of symptoms and severity if any of the symptoms experienced), in addition to patient preference concerning the two bandage brands at the end of the crossover trial when both brands had been worn. Any adverse events, withdrawal, loss to follow-up and VLU infection rates were also recorded. Serious adverse events were pre-defined in the protocol, and the study was managed in accordance with good clinical practice.

Statistical analysis

Since pruritus has been reported as an undesirable effect by patients (Reich-Schupke et al, 2009), and one of the compression bandages in the trial contains calamine with the aim of controlling this feature, this was used for a priori sample size calculations. With no pilot data available, a hypothetical distribution of responses on the SPS was used for sample size calculation purposes. The estimated clinically important difference for SPS is 20% (Yosipovitch et al, 2017). A minimum of 25 patients needed to be enrolled to achieve 80% power with 5% significance, based on one-point difference between two different bandages when measured on a 5-point Likert scale for SPS. To allow comparative analysis of data before and after the crossover period, a per protocol approach was applied. The Mann-Whitney U-test was applied for the outcome measures for individual time points, whereas the Wilcoxon signed-rank test was used for paired analysis of combined week 3 and week 6 outcome data. Carryover effect was calculated by performing the Wilcoxon test on the sum average for the Andoflex TLC Calamine-first group versus the Coban2-first group. Treatment effect was assessed by performing the Wilcoxon test on the difference between week 3 and week 6 outcomes for the Andoflex TLC Calamine-first group, and the difference between week 6 and week 3 data for the Coban2-first group (Koch, 1972). Analysis for period effect was not performed because of the relatively short intervention periods. Data were collated using MS Excel software and analysed using SPSS v20.

Results

From February 2019 to and including November 2019, 61 patients were considered, of which 39 patients were randomised (*Figure 1*). The vascular department enrolled 36 patients, and each of the three GP practices recruited one patient; recruitment was ended since the planned target had been reached (it was exceeded due to presentation of more suitable patients than anticipated in the planned enrolment period). A total of 35 of 39 (90%) patients completed the 6-week two-phase trial period. A single adverse event occurred, where a patient had to be taken off AndoFlex TLC Calamine due to a mild skin reaction, which could probably be attributed to the bandage. *Table 1* provides an overview of baseline patient characteristics for each respective 'first treatment' randomisation arm and for the study cohort as a whole. Patients who first commenced on AndoFlex TLC Calamine were on average younger, but otherwise the treatment arms were similar. All participants, bar one, were instructed to wear the compression bandaging continuously in line with clinical needs. *Table 2* shows how the performance of AndoFlex TLC Calamine compared with Coban2 as measured using validated questionnaires. These included measurement of pruritus (SPS tool, visual pruritus score and 5D itch score), patient-reported quality of life in relation to their chronic venous insufficiency (CIVIQ20), clinician score of severity of the patient's vascular disease (VCSS) and a semi-quantitative PUSH score on venous ulcer size.

No significant carryover effect was observed for any of the outcome measures. The treatment effect observed for SPS was also non-significant at 0.24. Therefore, no significant difference in pruritus levels was observed between the compression bandage systems. Similarly, no significant difference was observed for the other two validated pruritus measurement tools. In the case of the non-itchiness measures—ulcer size, venous disease symptoms and quality of life—a smaller score indicates a more favourable outcome. As seen in *Table 2*, a significant treatment effect was observed for Andoflex TLC Calamine versus Coban2 in relation to PUSH score and VCSS. This suggests that Andoflex TLC Calamine may be associated with accelerated improvement in the clinical features of VLUs.

Non-validated surveys were administered to participants when compression bandage was applied for the first time and at the end of each 3-week period. The instant reaction surveys were non-informative, since all patients reported positively about the comfort and fit of the bandaging, regardless of the applied brand. At the end of the trial period for each bandage, the participants were asked to report whether they experienced symptoms that may be associated with wearing compression bandaging, and what the frequency and severity of these symptoms were while wearing each brand of compression bandaging (responses for each brand of compression bandaging from the pre- and post-crossover trial phases were merged). Of the 11 symptoms assessed, 'pins and needles' were almost never experienced by any participant, sweating was a rare occurrence and there were no patient-reported difficulties getting dressed with either bandage. Hardly any patients felt a degree of heaviness or burning sensation while wearing either compression bandage. *Figures 2* and *3* summarise the data for the remaining six symptoms that were investigated. Itchiness was confirmed as the most common symptom experienced by patients, followed by three other symptoms: a sensation of constriction; pain; and movement restriction. Patients experienced pruritus more often when wearing Coban2, and the symptoms were more troublesome. Coldness was a symptom experienced when wearing AndoFlex TLC Calamine in particular, although the symptom was deemed mild.

To explore if there were any signs of impact on wound healing by either of the compression bandage brands, the PUSH score was recorded for all participants (score of nil for patients without an ulcer) at baseline, week 3 and week 6. Although the leg ulcers in the cohort that used AndoFlex TLC Calamine first were on average significantly larger, this

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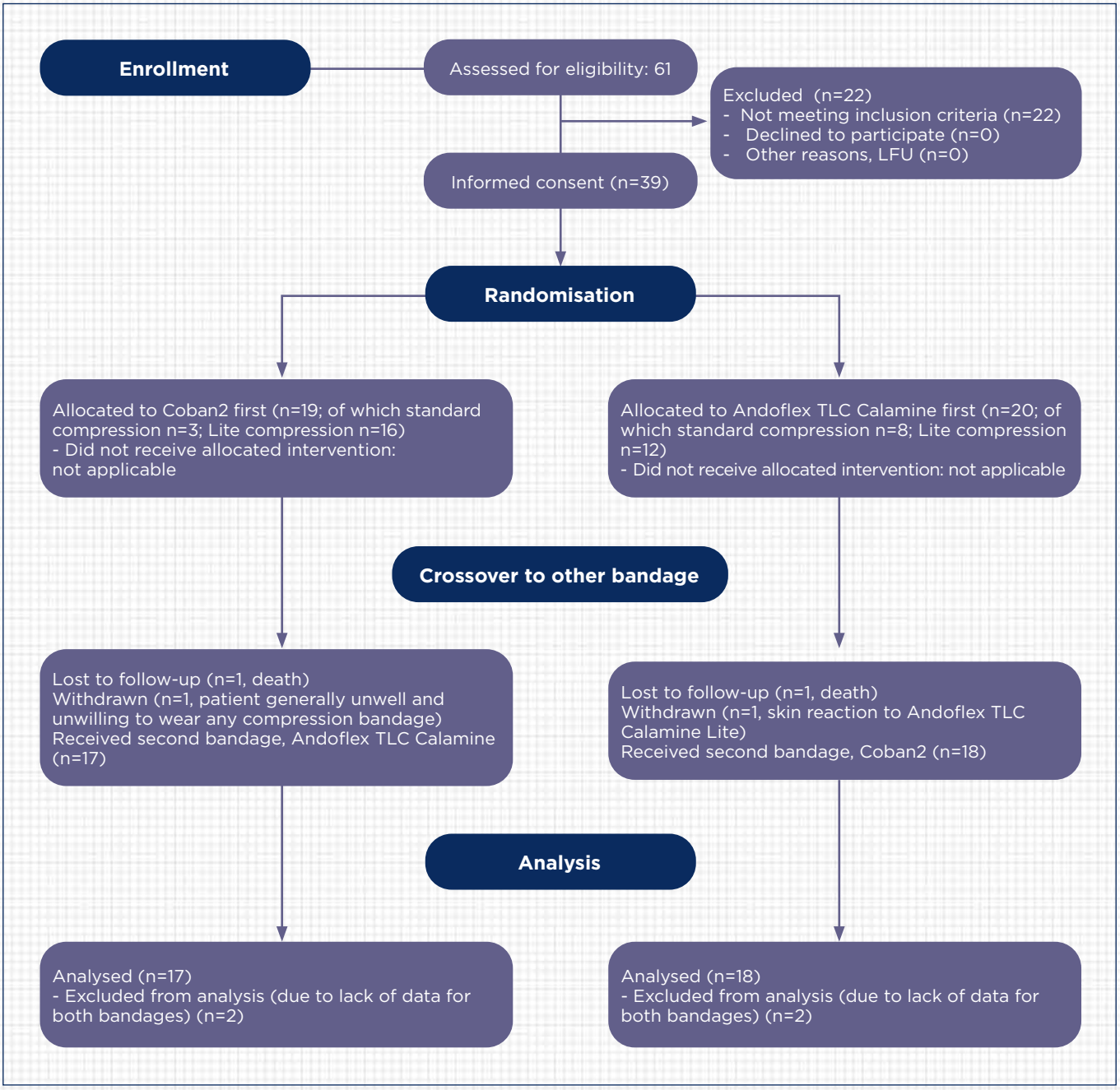

Figure 1. CONSORT flowchart for APRICOT trial

difference reduced to a non-significant difference versus the Coban2 cohort by the end of week 3. However, when AndoFlex TLC Calamine was used post-crossover, a non-significant improvement versus Coban2 was observed both versus the other cohort within that timeframe and versus the pre-crossover period involving the same cohort of patients.

Figure 4 summarises the responses by patients concerning their preference for any of the two compression bandage brands that they wore in the preceding 6 weeks. Q1–Q9 correspond to the nine questions in *Box 1*. Overall, more patients preferred AndoFlex TLC Calamine; from a patient viewpoint, it appears that the degree of comfort offered by AndoFlex®TLC Calamine was the main reason they preferred it over Coban2 (Q3, Q5 and Q9), with pruritus control being a secondary reason (Q5). Patients were also offered the chance to write additional comments about their experience with the two compression bandages. The most common free-text patient comments associated with wearing AndoFlex TLC Calamine were that it felt 'cooling' (mentioned six times) and 'soothing' (noted five times). These observations were not made by patients when they wore Coban2. A total of five nurses applied both compression bandage brands to the trial participants' legs. At the end of the trial, they were asked whether they had a preference regarding the bandages. On a 5-point Likert scale, three nurses 'probably' preferred and two nurses 'definitely' preferred to use AndoFlex TLC Calamine over Coban2.

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Discussion

Significant advances have been made in compression bandage technology, particularly with the progression from four-layer to two-layer designs. Unna's boot is a four-layer compression bandage treatment option that has since been surpassed in popularity by two-layer short-stretch designs due to the ease of application, although respective wound healing efficacy is similar (Ashby et al, 2014; De Carvalho et al, 2018). AndoFlex TLC Calamine revisits the use of calamine as in Unna's boot but in the modern two-layer compression bandage design, and the present study assessed patient feedback regarding this product versus the established Coban2 brand through a randomised crossover trial. This study showed that: (a) pruritus is the most common and most bothersome symptom associated with wearing compression bandaging; and (b) AndoFlex TLC Calamine was preferred by patients for the degree of comfort provided, but no significant difference was observed in this study versus Coban2 when validated outcome measures for pruritus were applied.

AndoFlex TLC Calamine was preferred over Coban2 by most participants in this study, possibly due to the reduced itchiness and cooling or soothing effect reported by participants. A degree of carryover effect, a known risk in crossover studies where no washout period is possible (Mills et al, 2009), may have occurred, since the carryover p-values for pruritus surveys were close to the significance level of 0.05. Although the difference in pruritus levels between the two bandage brands was less obvious according to the outcomes measured using validated scales for itchiness, the anti-pruritic effect of Unna's boot has been demonstrated before in patients with sulphur mustard exposure. Zinc oxide, the main ingredient of calamine, is a recognised anti-pruritic agent and, similar to calamine itself, it is applicable for a multitude of disorders (Mak et al, 2013; Gupta et al, 2014). Impregnation of textiles with zinc oxide, akin to the AndoFlex TLC Calamine approach, is an emerging therapeutic modality for atopic dermatitis, for example (Wiegand et al, 2013). In a previous study, two-layer Coban2 was found to be preferred to the four-layer Profore system (Moffatt et al, 2008), although pruritus was not assessed; bandage slippage was the key outcome measure in that study. In the present investigation, the degree of bandage slippage was comparable between AndoFlex TLC Calamine and Coban2 and less of an issue than itchiness, leg constriction and pain.

The outcomes for wound size (PUSH), clinical severity of venous disease (VCSS) and vascular-related patient quality of life (CIVIQ20) were favourable for AndoFlex TLC Calamine, with significant differences found for the former two. However, this has to be placed in context of the study design and applicable inclusion and exclusion criteria. The crossover design means that both 'Lite' and full compression patients could be enrolled in the trial, since they were allocated the same

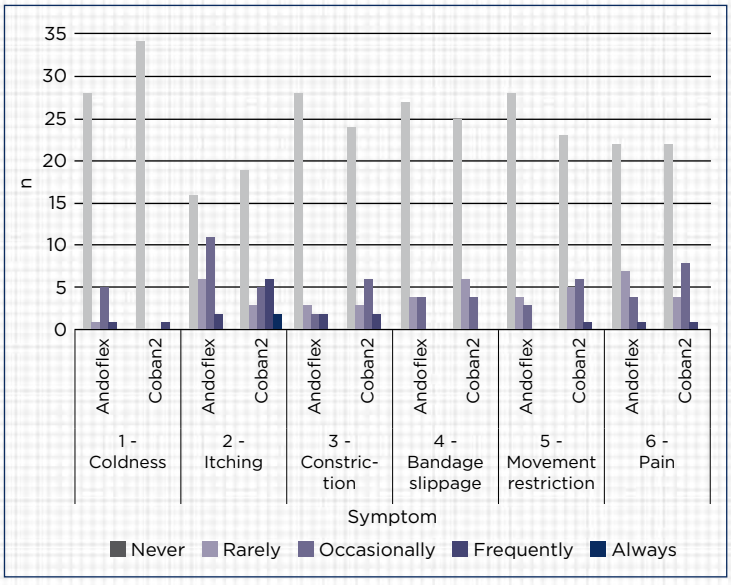

Figure 2. Reported frequency of six symptoms

Table 1. Demographics and clinical parameters at baseline (trial completers only; normal and Lite compression patients combined)

	Cohort		
Variable	Coban2 first (n=17)	Andoflex TLC Calamine first (n=18)	Complete study population (n=35)
Age in yrs, mean (95% CI)	78 (74 to 82)	70 (63 to 77)	74 (69 to 78)
Sex, male (%) / female (%), n	8 (47%) / 9 (53%)	9 (50%) / 9 (50%)	17 (49%) / 18 (51%)
Body mass index in kg/m^2, mean (95% confidence interval)	31 (27 to 35) (n= 16)	32 (29 to 36) (n= 14)	32 (29 to 34) (n=30)
Smoking status, never / ex / current, n	9 / 4 / 1 (n= 14)	10 / 2 / 2 (n= 14)	19 / 6 /3 (n= 28)
Reason for compression bandaging, ulcer / post-surgery / conservative, n	13 / 2 / 2	16 / 1 / 1	19 / 3 / 3
Mobility status, w/o assist / w assist / unable to walk	8 / 4 / 3 (n=15)	9 / 6 / 0 (n=15)	17 / 10 / 3 (n =30)

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compression strength for each of the two bandage brands. Since the primary objective was to assess pruritus and other patient-reported symptoms associated with compression therapy, some patients without ulcers were also included in the trial. An efficacy trial for wound healing and venous insufficiency symptomology is indicated to determine whether the improved patient-reported comfort levels and indications of favourable healing associated with AndoFlex TLC Calamine truly translate into a positive clinical response. In the present study, wound size was not quantified using wound tracing or digital measurement for pragmatic reasons in, but it would have to be applied in a formal wound healing trial. Another limitation of this study is a lack of blinding of participants and/or the use of a blinded metrologist. Further, although patients were recruited from different sites, most (92%) were recruited from a single site.

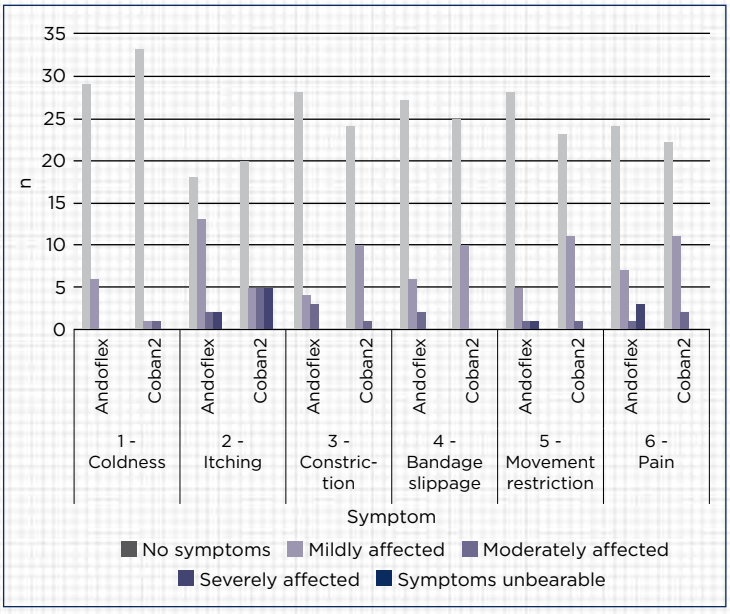

Figure 3. Reported severity of six symptoms

This study has identified key patient-reported issues that may arise from wearing two-layer compression bandaging. Itchiness of the legs appears to be the main issue. The feeling of constriction, pain and movement restriction may occur with either AndoFlex TLC Calamine or Coban2, and one bandage may yield better results than the other in those situations. Previous publications have reported that pain associated with having a leg ulcer is an issue, and that the degree of mobility while wearing compression bandaging is an important consideration for patients (Walshe, 1995; Morgan et al, 2011). Since in all patients but one, the compression bandaging was to be worn continuously, the impact of each bandage brand on therapy compliance rates was not assessed. However, compliance is a recognised issue. Since a possible reaction to AndoFlex TLC Calamine was seen with one patient, a patch test with the base layer could be performed if there are any concerns regarding adverse reactions. However, published cases of reactions to calamine are rare and usually involve the presence or application of another substance (Praditsuwan et al, 1995; Gupta et al, 2007). In the present study, related to

Table 2: Measurement and comparison of outcome measures between Coban2® and AndoFlex® TLC Calamine

	Baseline, week 0			Week 3 (pre-crossover)			Week 6 (post-crossover)			Crossover analyses	
Outcome measure	AndoFlex® first (n=18)	Coban2® first (n=17)	p-value*	AndoFlex® (n=18)	Coban2® (n=17)	p-value*	Coban2® (n=18)	AndoFlex® (n=17)	p-value*	Carryover effect, p-value**	Treatment effect, p-value**
Severity of pruritus score, median (IQR)	0.5 (0–1.3)	1 (0–2.5)	0.30	0 (0–1)	1 (0–2.5)	0.10	0 (0–1.3)	1 (0–1)	0.26	0.10	0.24
Visual pruritus scale, median (IQR)	2 (0–5)	5 (0–6)	0.35	0 (0–3)	4 (0–6)	0.28	0 (0–4)	1 (0–4)	0.26	0.17	0.23
5D itch score, median (IQR)	8.5 (5–12)	10 (5–14)	0.38	5 (5–9)	7 (5–12)	0.18	5 (5–9)	7 (5–10)	0.20	0.12	0.36
PUSH, median (IQR)~	10 (8–12.5)	8 (2.5–9)	0.010	10 (1–12.5)	7.5 (0–11)	0.54	7 (0–10)	0 (0–9)	0.15	0.49	0.002
VCSS, median (IQR)+	13 (10–17)	12 (11–17)	0.61	11 (7–16)	11 (8–13)	0.97	11 (5–14)	8 (5–12)	0.39	0.64	<0.001
CIVIQ20, median (IQR)	54 (31–74)	61 (46–67)	0.61	44 (25–61)	49 (29–54)	0.59	43 (23–54)	38 (29–54)	0.90	0.88	0.055

~ AndoFlex® n=17, Coban2® n=16; + AndoFlex® n=17, Coban2® n=17; *Mann-Whitney U-test; ** Wilcoxon signed-rank test; IQR=interquartile range; PUSH=Pressure ulcer scale for healing;VCSS=Venous clinical severity score; CIVIQ20= Chronic venous disease quality of life questionnaire

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tolerability, one patient who could only tolerate Coban2 for two days before having it changed could manage to wear an AndoFlex TLC Calamine bandage for four consecutive days.

Conclusion

In conclusion, from a comfort perspective, AndoFlex TLC Calamine was preferred to Coban2 compression bandaging by the study participants. Pruritus levels appeared low with AndoFlex TLC Calamine, which supports the rationale of introducing calamine in two-layer short stretch compression bandaging technology; however, the difference in pruritus levels as measured using validated outcome measures were non-significant compared with Coban2.

Further research is indicated to further explore the potential of AndoFlex TLC Calamine to aid leg ulcer healing and wider clinical outcomes, through a non-crossover randomised controlled trial design, with stratification by degree of compression ('Lite' and full compression), exclusion of patients without ulcers and a longer trial phase of, for example, 12 weeks. The putative contributory role of patient compliance with compression therapy should also be explored. **cwc**

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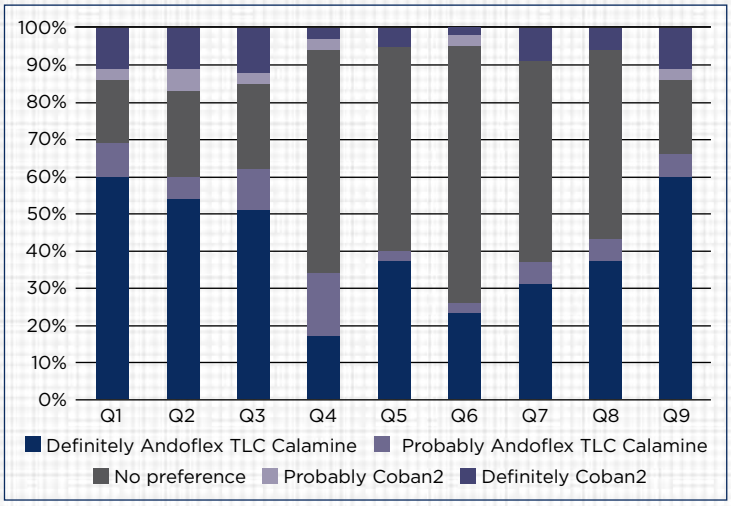

Figure 4. Patient responses on bandage preference

Box 1. Patient preference survey questions asked at the end of the trial (results summarised in *Figure 4*)

1.	Overall, the bandage of my preferred choice is:
2.	I would recommend the following bandage to other patients:
3.	The bandage that was most comfortable to wear was:
4.	The bandage easiest to apply to my leg(s) - or applied by someone else - was:
5.	The bandage that was easiest to move about in was:
6.	The bandage that allowed me to use normal footwear/shoes the best was:
7.	I had the least itchiness problems with:
8.	I had the best night rest when I was using the following bandage:
9.	The bandage that was the most comfortable for my skin was:

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KEY POINTS

- Compression bandaging of the lower legs, using a two-layer short-stretch system, is a core treatment modality for patients with leg ulcers due to chronic venous insufficiency
- Minimising patient discomfort related to compression bandaging is important to reduce the risk of non-compliance with compression therapy
- AndoFlex TLC Calamine is a compression bandage system similar to Coban2 in terms of the degree of compression achieved; it does however, contain calamine in the skin-touching base layer
- In this crossover trial, patients found AndoFlex TLC Calamine more comfortable than Coban2; however, no significant difference was found when this was measured using validated pruritus scales
- Further research is indicated to investigate whether AndoFlex TLC Calamine can contribute to enhanced venous leg ulcer healing rates

CPD REFLECTIVE QUESTIONS

- Of the symptoms associated with two-layer compression therapy, evaluated through patient feedback in this study, which are the most common and most severe?
- What aspects of compression therapy are important to patients and may contribute to improved compliance?
- How may calamine impregnated bandage contribute to controlling undesirable symptoms associated with compression therapy?

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