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A Clinical Investigation to Evaluate the Safety and Performance of a Novel Self-Administered Treatment Kit for Ingrowing Toenail

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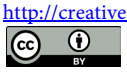

Abstract

Background: Ingrown toenail often results in a painful cycle of infection and inflammation and can affect the ability to go about everyday activities. In the UK and Europe, there are limited ways to prevent the development of ingrowing toenail without specialist intervention. Treatments are often invasive and may require periods of time off work. This prospective, single-site, non-comparative clinical study evaluates the performance, safety and convenience of a treatment kit that can be applied at home at the earliest signs of ingrowing toenail. **Methods:** Patients (n = 36) with mild ingrowing toenail used the Scholl Ingrowing Toenail Treatment kit for 6 weeks, with assessments by study investigators at Days 0, 21 and 42. The kit comprised a set of toenail clips and a spray, correct use of which was monitored at site visits and through patient diaries. **Results:** All patients enrolled in the study completed the 42-day treatment period. Severity of ingrowing toenail was significantly reduced in 88.9% (95% CI: 78.62, 99.15) of patients at the end of the study. Twenty-two patients (61.1%) exhibited full resolution of ingrowing toenail at Day 42 and none showed an increase in severity. Reduction in pain and severity of ingrowing toenail from baseline was significant at Days 21 and 42 ($p < 0.0001$). 63.9% of patients reported reduced discomfort and trauma using the treatment kit on the first day of treatment, which increased to 97.2% at the following visits. No serious adverse events or device events were reported. Most patients reported that the clips were convenient to use and did not impede their daily activities. **Conclusions**: The ingrowing toenail treatment kit was convenient and easy for patients to use at home and resulted in reduced pain and severity of ingrowing toenail at early stages of the condition.

Keywords

Ingrowing Toenail, Onychocryptosis, Ingrown Toenail, Non-Surgical,

Self-Treatment

1. Introduction

Ingrown toenail, also known as "onychocryptosis" or "unguis incarnates", occurs when the skin around the nail, or nail fold, is punctured or traumatized by one of the distal angles of the nail plate [1] [2]. The result is often a cycle of infection, inflammation and repair processes that develop into a painful, draining lesion with granulation of tissue at the side of the puncture [2].

1.1. Prevalence and Incidence of Ingrowing Toenail

Around 20% of patients presenting to their doctor with a foot complaint have an ingrown or ingrowing toenail [1]. The condition is common in the general population, with some studies reporting prevalence of 2/1000 patients in Australia [3] and 54/10,000 patients in the Netherlands [2] [4].

Incidence in the United Kingdom (UK) is reported to be 10,000 new cases per year [5]. Ingrown or ingrowing toenails are observed in people of all ages but are more common in those aged 16 - 25 years [6] [7]. People with diabetes have been found to have a higher incidence of ingrown toenails compared with the general population [8].

1.2. Etiology of Ingrowing Toenail

Ingrown or ingrowing toenails usually affect the hallux and less frequently affect the smaller toes [9]. The most important risk factor for developing an ingrown toenail, especially in younger patients, is improper trimming of the nails [5]. A study in Portugal found this to be evident in 63% of cases, while sweaty feet, wearing constricting footwear and rotation of the toe were also significant predisposing factors [10].

1.3. Measuring Severity of Ingrowing Toenail

Ingrowing or ingrown toenails have long been classified into three stages of increasing severity, pain and disability: Stage I, where there is inflammatory swelling and redness of the skin (erythema) around the affected nail; Stage II, where there is inflammatory secretion; and Stage III, where there is clear formation of granulation tissue around the invading nail edge [11]. A recent modification of this scale takes into account whether there was a greater contribution of the nail fold in the etiology of the condition at Stage II and suggests alternative treatment strategies accordingly [12]. It is generally accepted that ingrowing toenail is not a self-limiting condition and that toenails at Stage I will progress to Stage II and then Stage III if left untreated [2].

1.4. Procedures and Complications of Ingrown Toenails

Once an ingrown nail has become established, the site of puncture of the pe-

riungual skin experiences a cascade of inflammatory, infectious and reparative processes, causing an overgrowth of granulation tissue that forms a painful, draining, often foul-smelling lesion [9]. The pain of the ingrowing toenail can become so severe that it is disabling, affecting the normal activities of daily life, like going to school or to work [13].

At this point surgical treatment options are required and typically involve the removal of the troublesome part of the nail (partial or total nail avulsion) along with destruction of the nail matrix (matricectomy) and/or resection of the overlapping nail fold to prevent recurrence [7].

1.5. Standards of Care for Early Stage Ingrowing Toenail

At the early stages of ingrowing toenail a conservative treatment strategy is preferred, with professional nail cutting by a podiatrist as needed and advice for an appropriate regimen of self-care [7]. Conservative care includes warm daily soaks in hypertonic solutions (e.g. Epsom salts), and packing, lining or lifting techniques (e.g. cotton wool, dental floss or cyanoacrylate glue) [1] [7] [14]. Bracing the toenail, or orthonyxia, is a more invasive technique that usually involves the placement of a shaped metal wire over the affected nail to encourage it to grow out straighter, usually after trimming of the affected nail [2] [15] [16]. Avoidance of tight or ill-fitting shoes and of overzealous nail trimming is also important aspects of a conservative treatment regimen [13].

Although the aforementioned studies cited for orthonyxia have reported favorable patient outcomes, these techniques require application by a qualified healthcare professional [2] [15] [16]. An optimal treatment for ingrowing toenail should result in low recurrence, low morbidity, little pain and a good cosmetic effect whilst also being low-cost, technically easy to perform and have minimal effect upon daily life [15].

The intention of this study was to demonstrate the safety, efficacy and convenience of an orthonyxia-type treatment kit for early stage ingrowing toenail that can be self-administered by patients to reverse or prevent progression of the condition. The treatment kit is intended to be easily applied, with minimal inconvenience, by patients themselves at the earliest stages of ingrowing toenail. Early intervention in this manner may reduce the likelihood of a toenail becoming ingrown, thus avoiding the more severe complications of infection and surgical procedures [17].

2. Methods

2.1. Study Design

This was a prospective, single site, non-comparative clinical study (NCT02131363) evaluating the safety, utility and performance of the Scholl Ingrowing Toenail Treatment kit in patients with mild ingrowing toenail, as described by the Mozena Classification System (**Table 1**). Patients with an ingrowing toenail at Mozena Stage I used the Scholl Ingrowing Toenail Treatment kit for 6 weeks with

three visits to a clinic for assessments by study investigators at Days 0, 21 and 42. The convenience and ease of use of the treatment kit was also examined. The treatment kit is designed to halt and reverse the progression of the severity of ingrowing toenail, so any patient presenting with a toenail already ingrown was not considered eligible for this study.

2.2. Ethical Considerations

The methods and procedures used in this study, together with patient information and consent documents, were reviewed and approved by East of Scotland Research Ethics Service REC 2 (reference number 14/ES/0070), Tayside Medical Sciences Centre, Ninewells Hospital and Medical School, Dundee, DD1 9SY, UK. This study was conducted in accordance with ISO 14155:2011 [18] and the ethical principles of the Declaration of Helsinki, as referenced in European Union Directive 2001/20/EC, and complied with International Conference on Harmonisation Good Clinical Practice and all applicable regulatory requirements.

2.3. Recruitment

On the initial visit to the investigational site (Day 0) patients underwent a physical exam to establish the severity of their ingrowing toenail and any concurrent medical issues. A medical and social history was also taken to ensure each patient met the inclusion/exclusion criteria (Table 2). A key part of the inclusion criteria was that affected toenails must be rated as either "slightly ingrowing", "somewhat ingrowing" or "very ingrowing" on the Investigator Ingrowing Toenail Severity (IITS) scale. To avoid bias the investigators were advised to try and equalize the numbers of patients included across the three levels of severity.

Table 1. The Mozena Classification System for treatment of ingrown nails [12].

Stage	Signs and symptoms	Treatment
I	Erythema, slight edema and pain pressure is applied to the lateral fold	Conservative
IIa	Increased Stage I symptoms, drainage and infection, nail fold less than 3 mm	Conservative and/or matricectomy with hypertrophic ungual labia fold reduction
IIb	Increased Stage I symptoms, drainage and infection, nail fold 3 mm or greater	Same as Stage IIa
III	Magnified Stage II symptoms, presence of matricectomy with hypertrophic ungual labia fold granulation tissue and nail fold hypertrophy	Matricectomy with hypertrophic ungual labia fold

Table 2. Inclusion and exclusion criteria for enrolment of patients in this study.

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years (male or female) • Informed consent obtained • Patients presenting with one great ingrowing toenail rated as either "slightly ingrowing", "somewhat ingrowing" or "very ingrowing" on the IITS scale • Score of at least 3 on the Subject Pain Intensity (SPI) scale on at least 1 day of the preceding week • The affected toenail must have a minimum 2 mm of distal edge and a minimum nail width of 16 mm • Patients should be willing and able to take part in the study for the full 6 weeks and be able to understand the information provided to them	• Any other toenail pathology (including pincer or spicule toenail) • Previous participation in this study, or any other clinical study in the previous 30 days • If patients are immunocompromised or suffer from impaired feeling in the feet due to diabetes, peripheral vascular disease or neuropathy • Any cutaneous pathology or cuts/abrasions that could compromise safety or affect the outcome of the study (e.g. interfere with assessments) • Known sensitivity/allergy to any component of the treatment kit • Significant current or past medical history of hepatic, renal, cardiac, pulmonary, digestive, hematological, neurological, locomotor or psychiatric disease • Concomitant medication that might affect the response to the treatment or confuse the results • Patients must not be on regular pain relief and must not take any analgesics in the 24 hours before any onsite visit • Patients whose situation would, in the view of the investigators, interfere with optimal participation in the study or be at special risk in doing so • Female patients of childbearing age not willing or able to take adequate contraceptive precautions or abstain from sexual activity • Female patients who are currently pregnant or a lactating mother

2.4. Intervention under Investigation

The Scholl Ingrowing Toenail Treatment kit is an over-the-counter intervention for the relief and prevention of ingrowing toenail. The kit consists of three components: 10 acrylonitrile butadiene styrene (ABS) plastic toenail clips (enough to allow use of one clip per week for 6 weeks and four spare clips to allow for replacement due to detachment or breakage), 3 g of nail adhesive (to affix the clip to the toenail) and a 17 g, 22 mL can of cooling aerosol spray.

After cleaning and drying the affected toenail, patients first apply the aerosol spray, then a thin layer of the nail adhesive is applied to the top of the nail and then the clip is slid into place. The design of the clip means it should not prevent the patient wearing their usual day-to-day footwear such as socks and shoes for the duration of the study. The edges of the clip are hooked under each side of the nail before centering and gentle pressure applied to allow it to engage with the adhesive.

Though the clips are small, the shape and rigidity are designed to exert enough force to lift the edges of the affected toenail away from the skin (**Figure 1(A)** and **Figure 1(B)**), relieving pressure on the nail folds and allowing the nail to grow out straight.

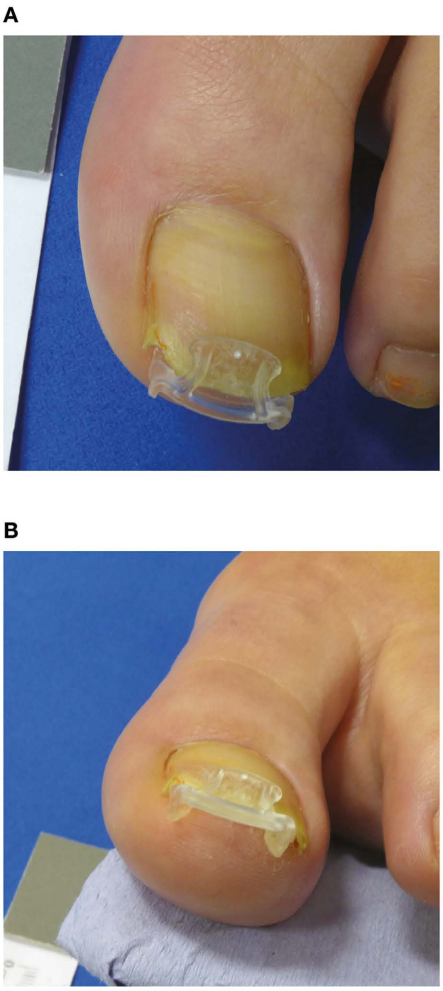

Figure 1. Fit and placement of the toenail clip as seen from above (panel A) and from the front (panel B) of the affected toe. The clip gently lifts and supports the nail edges to prevent penetration of the skin.

The cooling aerosol spray contains 40% ethanol to elicit a cooling effect (due to rapid evaporation) that should soothe the discomfort associated with the affected toenail. This is to be applied before application of the nail clip and as needed during periods of wear, at least once per day and not more than five times a day, with at least an hour between uses. For this study, acetone-based nail varnish remover was also provided to patients to facilitate the removal of toenail clips.

2.5. Study Protocol and Data Collection

Once enrolled, the patients received instruction on the use of the treatment kit and were observed while fitting their first nail clip. Patients were supplied with sufficient clips to last between site visits, a patient daily diary to record every removal and replacement of clips and were informed of the study protocol. The diaries were used to ensure compliance with the study protocol and to report

any adverse events (AEs) or the use of any concomitant medications. Patients were required to use the nail clips continuously for 42 days (6 weeks), applying the spray daily as needed (at least once per day and not more than five times a day, with at least an hour between uses) and replacing the nail clip every week. Clips could be removed under certain circumstances where they might be contraindicated, such as sporting activities, with the caveat that they be replaced soon afterwards.

Investigators evaluated treatment progression by physical and visual assessment of the nail and the risk presented to the nail fold during investigational site visits at the start (Day 0), middle (Day 21) and end (Day 42) of the treatment period. Investigators conducted follow-up interviews by phone on Days 2 (±1 day), 7, 14, 28 and 35 (all ±2 days). In addition to monitoring severity of the ingrowing toenail between site visit days, investigators used these interviews to enhance patient compliance with the investigation protocols, repeat any instructions for use of the kits and collect feedback on utility of the treatment kit.

Existing scales for assessing the severity of ingrowing toenail do not permit much differentiation of mild, early symptoms before the nail penetrates the skin. To enable stratification of patients enrolled in this study and to accurately monitor the progression of symptoms leading up to an ingrown toenail, the IITS scale (Table 3) was developed in collaboration with Dr. Farina Hashmi, Prof. Christopher Nester and Michael Harrison-Blount at the University of Salford. This scale was developed specifically for use in this study and has not been externally validated. The IITS scale takes into account the level of discomfort due to the angle of nail growth, skin integrity, redness, the amount the nail presses on the nail fold and the intensity of pain. This allowed the investigators to consistently establish the severity of potentially ingrowing toenails at Mozena Stage I on a scale from 0 ("not ingrowing") to 4 ("ingrown"). To meet inclusion criteria, patients were required to present with ingrowing toenails rated as 1 ("slightly ingrowing"), 2 ("somewhat ingrowing") or 3 ("very ingrowing").

Patients were also required to report the most intense pain suffered at any time in the 7 days prior to the site visit using an 11-point Subject Pain Intensity (SPI) scale (Table 4), which ranged from 0 (no pain), through 5 (moderate pain) and up to 10 (worst pain imaginable). A minimum score of 3 was required to meet the inclusion criteria.

Table 3. Investigator Ingrowing Toenail Severity (IITS) scale.

Severity scale	Severity scale code	Pain intensity	Skin integrity	Pressure of nail curvature on nail-fold	Redness	Discomfort incidence
Ingrown	4	Severe	Breached	Tightly pressed	Severe	Continuous
Very ingrowing	3	Moderate	At risk of breaching	Clearly presses	Moderate	Most of the time
Somewhat ingrowing	2	Mild	Skin intact	Pressing but can be pulled away	Mild	Some of the time
Slightly ingrowing	1	Some	Skin intact	Some risk	Some	Occasionally
Not ingrowing	0	None	Skin intact	No risk	None	None

Table 4. Subject Pain Intensity (SPI) scale used to evaluate severity of pain experienced by patients.

0	1	2	3	4	5	6	7	8	9	10
No pain					Moderate pain				Worst pain imaginable	

Patient feedback on the performance and utility of the intervention was collected by means of a questionnaire 30 mins after application of the first nail clip on Day 0, then again during the follow-up visits on Day 21 and Day 42. Patients were asked to respond to various questions regarding their experience of using the treatment kit using a 5-point agreement scale ("Strongly Agree", "Agree", "Neither Agree nor Disagree", "Disagree" and "Strongly Disagree").

During the follow-up calls between site visit days, if there was a significant change in the severity of the ingrowing toenail, an unscheduled visit could be arranged to allow an investigator to examine the toenail and decide whether to continue treatment. Assessments carried out during unscheduled and scheduled site visits included: removal of the current nail clip for assessment of ingrowing toenail severity, recording the SPI score for the previous week, checking the patient diary for compliance and taking photographs of the affected toenail.

Standardized photographs were taken by investigators from the front and above the toenail, before and after application of the nail clips on Day 0 and Day 21, with a final photograph taken following removal of the last nail clip at the completion of the study on Day 42 (or earlier if the patient completed ahead of schedule).

If at any visit the toenail was observed to be "ingrown" the patient would be withdrawn from the investigation and the investigator would recommend a suitable alternative treatment. If investigators assessed that a toenail was "not ingrowing" according to the investigation criteria, then treatment was recorded as "complete" and final photographs of the toenail taken.

Safety was assessed based on AEs or adverse device events (ADEs) reported during the study period, either during site visits or the patient follow-up calls. All AEs and ADEs were rated "mild", "moderate" or "severe" and could be "definitely related", "probably related", "possibly related" or "not related" to the use of the treatment kit.

2.6. Primary and Secondary Endpoints

The primary endpoint was the percentage of patients that experienced a reduction in the severity of ingrowing toenail, assessed on the IITS scale, after 42 days of treatment.

Several other investigator and patient-derived secondary outcomes were also collected to assess clinical performance, ease of use and safety of the treatment kit. These comprised changes in the severity of ingrowing toenail and the severity of pain during the week preceding a site visit, and the percentage of patients whose ingrowing toenail severity stabilized at Day 21 and 42, or reduced at Day

21. Patients were asked how soon they experienced pain relief for their ingrowing toenail, whether the aerosol spray cooled and/or soothed their ingrowing toenail, if they could carry on with daily activities (e.g., wear socks and shoes as normal), if treatment was convenient and if it reduced the discomfort/trauma of the ingrowing toenail. The safety profile of the treatment kit was based on assessments of severity, frequency and seriousness of AEs or complications associated with the usage of the treatment kit.

2.7. Statistical and Data Analysis

The primary endpoint, the percentage of patients showing a reduction in the severity of ingrowing toenail, was expressed as the percentage of patients who demonstrated a reduction in the IITS score at Day 42 compared with Day 0, with a 95% confidence interval (CI) using the normal approximation. The null hypothesis was that the percentage of patients showing reduced severity would be less than 50%.

Analysis for secondary outcomes included: increase or decrease of IITS scores at Days 21 and 42 compared to Day 0, the percentage of patients with reduction in IITS scores at Day 21, the percentage of patients with IITS scores of 0 at Days 21 and 42, the change from baseline in patient's pain intensity, measured using the SPI scale at Days 21 and 42, and the percentage of patients who experienced pain relief under 10 seconds, 5 minutes or 30 minutes after application. Changes from baseline data were compared using the Wilcoxon signed rank-test to show changes from baseline values. The null hypothesis each time was that there would be no change from baseline.

Investigators also recorded the percentage of patients reporting levels of discomfort or trauma, and the percentage of patients that reported being able to wear their regular socks and shoes and carry out normal daily activities unimpeded. The duration of adhesion of the clip was also investigated based on the probability of completing a 7-day clip period using a mixed logistic regression model and was interpreted as the proportion of clips that stay on a nail for 7 days. AEs, serious AEs (SAEs), ADEs and serious ADEs (SADEs) were summarized with frequencies (n) and percentages.

At sample size of 30, the PROC Power procedure with the ONESAMPLFREQ option using SAS® version 9.2 showed that in order to achieve greater than 80% power for the success criteria, 75% of patients would have to demonstrate a reduction in ingrowing toenail. Calculating a potential dropout rate of 15%, a sample of size of 36 patients would ensure that enough patients made it into the primary analysis.

3. Results

3.1. Patient Characteristics and Demographics

A total of 65 patients were invited for initial screening at Day 0, with 29 failing to meet the inclusion criteria and 36 continuing to full enrolment, participation and completion (**Figure 2**). Of the 36 patients enrolled, 16 (44.4%) were male

and 20 (55.6%) were female. The mean age (±standard deviation [SD]) of patients was 51.4 (±13.5) years, ranging from 23 to 75 years (Table 5).

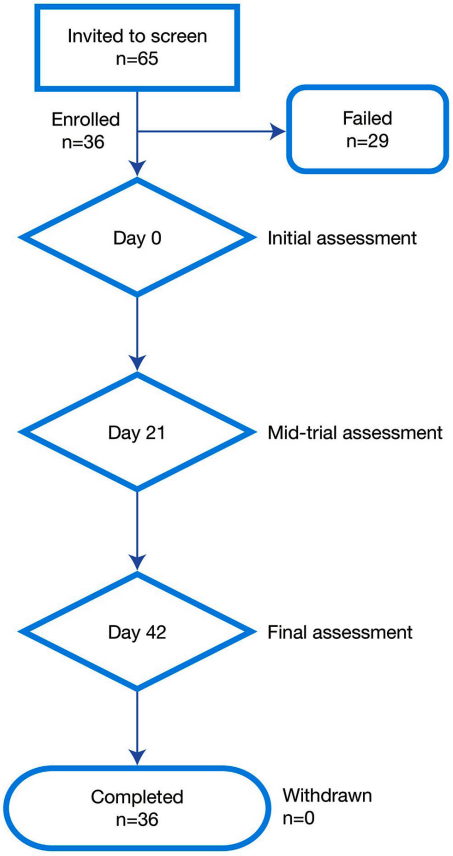

Figure 2. Overview of patients screened and enrolled in the study. From a total of 65 patients that were invited to screen, 36 were enrolled and completed the initial, mid-trial and final assessments.

Table 5. Demographics and baseline assessments of patients enrolled.

Demographics/assessments	Patients (n = 36)
Age (mean ± SD)	51.4 ± 13.5 years
Male	16 (44.4%)
Female	20 (55.6%)
Ethnicity	
Caucasian	34 (94.4%)
Asian	2 (5.6%)
Toenail severity (IITS score)	
Very ingrowing (IITS 3)	6 (16.7%)
Somewhat ingrowing (IITS 2)	21 (58.3%)
Slightly ingrowing (IITS 1)	9 (25.0%)
Subject Pain Intensity (SPI; mean ± SD)	5.8 ± 1.7
Min, Max	3.0, 9.0
Intention to Treat (ITT) population	36 (100.0%)

3.2. Primary Endpoint

Severity of ingrowing toenail was reduced after 42 days of treatment in 88.9% (32/36) of patients (95% CI: 78.62% - 99.15%) (Figure 3(A)). Severity of ingrowing toenail was unchanged in 11.1% (95% CI: 0.85 - 21.38) of patients.

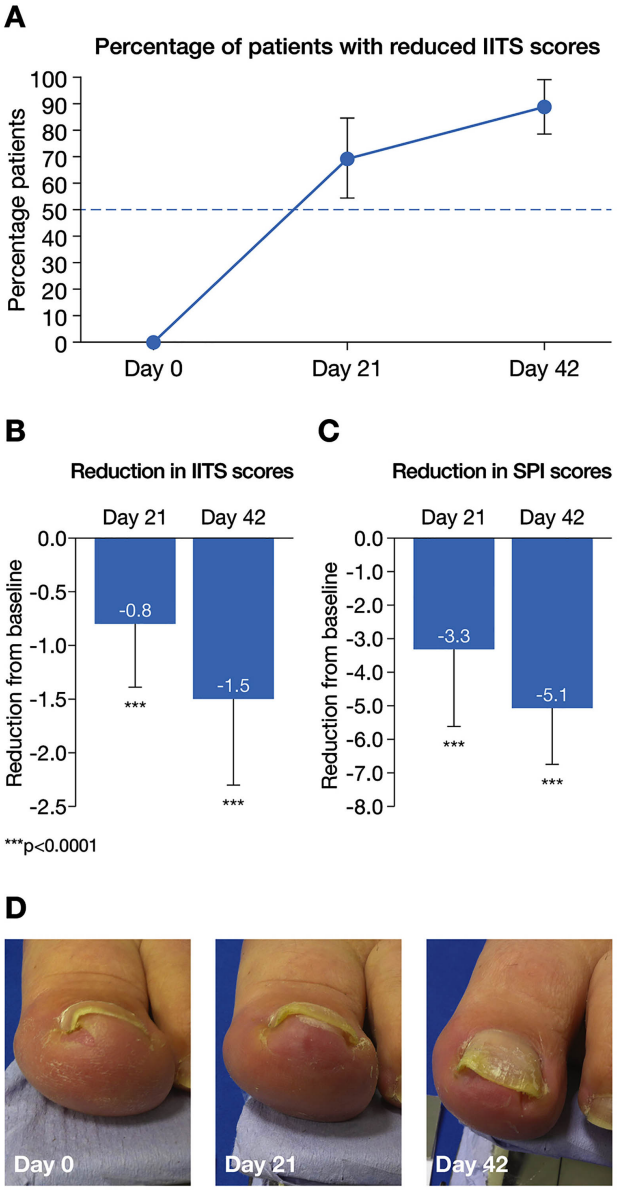

Figure 3. Effect of toenail treatment kit on severity of ingrowing toenail. Use of the ingrowing toenail treatment kit was associated with reduced severity of ingrowing toenail. The percentage of patients with reduced IITS scores exceeded 50% by Day 21. Values represent the percentage of patients with reduced IITS score and error bars represent the 95% CI (panel A). The reduction in IITS and SPI scores was statistically significant ($p < 0.0001$) after 21 and 42 days of use. Values represent mean change from baseline and error bars represent the SD (panels B and C). Photographs were taken on Day 0, 21 and 42 to record the reduction of ingrowing toenail.

3.3. Secondary Endpoints

There was no increase in IITS scores for any of the enrolled patients at either Day 21 or Day 42. Significant reductions in the IITS scores (mean ± SD) were observed at Day 21 (−0.8 ± 0.6, $p < 0.0001$) and Day 42 (−1.5 ± 0.8, $p < 0.0001$) when compared against baseline scores at Day 0 using the Wilcoxon signed rank-test (**Figure 3(B)**). Patients experienced significantly reduced values on the SPI scale (mean ± SD) at Day 21 (−3.3 ± 2.3, $p < 0.0001$) and Day 42 (−5.1 ± 1.7, $p < 0.0001$) when compared against baseline scores using the Wilcoxon signed rank-test (**Figure 3(C)**).

At Day 21, 69.4% (95% CI: 54.40% - 84.49%) or 25/36 patients had reduced IITS scores and 30.6% (95% CI: 15.51% - 45.60%) or 11/36 patients showed no change.

The percentage of patients with IITS score of 0 (toenail "not ingrowing") at Day 21 was 0%, and by Day 42 this was 61.1% (95% CI: 45.19% - 77.04%) or 22/36 patients with a resolved ingrowing toenail.

On the first day of treatment, 63.9% (23/36) of patients reported reduced discomfort and trauma of their ingrowing toenail, which increased to 97.2% (35/36) of patients by Day 21 and Day 42. Cumulatively, 69.4% of patients reported pain relief within 30 minutes of application (**Table 6**). At Day 21, 77.8% (28/36) of patients either "strongly agreed" or "agreed" that use of the clips and spray was convenient, 94.4% (34/36) either "strongly agreed" or "agreed" that they were able to wear their shoes and socks, and 97.2% (35/36) either "strongly agreed" or "agreed" that they were able to carry on with their daily activities. At Day 42, this percentage was 86.1% (31/36), 91.7% (33/36) and 100% (36/36), respectively. The mixed logistic regression model for predicting the duration of clip adhesion estimated that 49.5% (95% CI: 40.94% - 58.11%) of clips provided 7 days of wear for an average patient.

3.4. Safety Endpoints

A total of 19 AEs were reported for 13 (36.1%) patients, with the most frequently reported AEs by system organ class being "gastrointestinal disorders" in five (13.9%) patients and "nervous system disorders" in five (13.9%) patients. Investigators assessed 12 AEs as "mild" and seven as "moderate" in intensity.

Table 6. Cumulative data from the question "After using the ingrowing toenail treatment kit, when did you first experience pain relief?"

	Cumulative frequency (n = 36)	Cumulative percentage
"Less than 10 seconds"	14	38.9%
"Less than 5 minutes"	22	61.1%
"Less than 30 minutes"	25	69.4%
No data	11	100%

No SAEs were reported, and all AEs were considered to be unrelated to use of the treatment kit. Most of the AEs were reported in single patients, with the only preferred terms reported for more than one patient being "nausea" and "headache", experienced by three patients each.

A total of eight ADEs were reported for seven (19.4%) patients, with the most frequently reported ADE being "pain in extremity", experienced by four patients and the remaining ADEs being "contusion" (two cases), "nail injury" (one case) and "onycholysis" (one case). Investigators considered four ADEs as "mild" and four as "moderate" in intensity. No SADEs were reported and all ADEs were either "probably related" (two cases of "pain in extremity" and one case each of "contusion", "onychoclasis" and "nail injury") or "possibly related" (two cases of "pain in extremity" and one case of "contusion") to treatment with the ingrowing toenail kit. There were no deaths or other significant AEs/ADEs encountered in this study.

4. Discussion

The objective of this study was to provide information on the safety, efficacy and convenience of using a novel over-the-counter, self-applied treatment kit for prevention of ingrowing toenail over a period of 6 weeks. The Scholl Ingrowing Toenail Treatment kit used in this study comprises an ABS plastic clip that is placed on the distal edge of the affected toenail that was changed weekly and a cooling aerosol spray that was applied daily (as needed) to the affected toenail. The patient population targeted was those at the initial stage of ingrowing toenail (Mozena Stage I), prior to penetration of the skin by the nail edge, when the toenail would be considered "ingrown".

This study demonstrated that a statistically significant percentage of patients using the treatment kit recorded a reduction in the severity of ingrowing toenail after 21 days of use ($p < 0.0001$) that persisted to Day 42 ($p < 0.0001$). This reduction was seen in 88.9% of patients after 6 weeks of treatment. During the timeframe of this study, no patients experienced a worsening of their ingrowing toenail and 22 patients (61.1%) had their ingrowing toenails resolved by the last day of the study.

The results of the SPI assessments at Day 21 and Day 42 indicate that application of the nail clip was associated with a reduction in patient's pain intensity compared to baseline. Furthermore, over two-thirds (~70%) of patients experienced reduction in pain severity within 30 minutes of application, and almost all patients reported reduced discomfort and trauma by the end of the study.

Use of the nail clips was not considered an impediment to daily activities by almost all the patients, and the majority considered the kit a convenient means of treatment for ingrowing toenail and indicated that they were able to wear socks and shoes during the treatment period. Very few ADEs were associated with the use of the nail clips, none of which were considered "severe".

Conservative treatments for ingrowing toenail, such as taping or packing with

cotton and cyanoacrylate, are available and have demonstrated good recovery times [17] [19] [20]. The Scholl Ingrowing Toenail Treatment kit investigated in this study is intended to treat a milder condition of ingrowing toenail, when it is at a much earlier stage. The results presented in this study suggest that the nail clip can reduce the pain associated with early ingrowing toenail and prevent worsening of the condition.

Limitations

There were several limitations associated with this study. The study included a small sample size; however, according to the power analysis, 30 patients would be sufficient if 75% of patients responded to the treatment kit, and the results revealed the percentage of patients with reduced severity was 88.9%. Similar numbers of patients in trials of conservative methods have also been reported in the literature [15] [17] [21] [22] [23].

In addition, an untreated group was not included in this study. It is generally accepted that mild symptoms of ingrowing toenail will progress to more serious stages if left untreated [2], meaning that the use of an untreated control group would be difficult to justify for a clinical study. The lack of a conservative or a surgical care arm in this study means that it was not possible to compare the efficacy of the Scholl Ingrowing Toenail Treatments kit directly with current standards of care, a point which should be rectified in further studies.

This study only investigated the use of the nail clip in patients with ingrowing toenails, and patients with ingrown toenails were excluded from the study. Further studies would need to be carried out to investigate the use of the nail clip in this population. Furthermore, this study only followed patients up to 6 weeks from baseline. Therefore, a comparison against other conservative methods and an investigation of the rate of recurrence when using the treatment kit were not possible. The principal aims of this study were to demonstrate the benefits of this treatment paradigm for patients in terms of effectiveness, convenience and ease of utility. Further studies should look to incorporate a minimum 6-month period of follow-up to provide adequate time to measure symptomatic recurrence between different treatment methods and to investigate the use of the nail clip in more severe conditions [1].

The time period of treatment evaluated in this study (42 days) was insufficient to allow accurate assessment of the estimated median duration of treatment required to resolve ingrowing toenail. Therefore, further studies should look to evaluate the treatment kit over a longer period to enable a more accurate estimation of the time to resolution.

5. Conclusions

Use of the nail clips and aerosol spray of the Scholl Ingrowing Toenail Treatment Kit resulted in a significant reduction in the pain and the severity of ingrowing toenail at early stages of the condition. Pain relief was observed in the

majority of patients from the first application of the nail clip and aerosol, with resolution of the ingrowing toenail observed in ~60% of patients within 6 weeks.

The intervention was easy and convenient to self-administer without impacting upon daily activities, while demonstrating efficacy, utility and safety in a real-patient population. These data therefore suggest that the nail clip and aerosol spray are of benefit to those with ingrowing toenail, and that the kit is easy to use. It is therefore a welcome addition to the treatment armamentarium of ingrowing toenail that permits treatment at home in the early stages, helping to prevent further trauma.

Ethics Approval and Consent to Participate

The methods and procedures used in this investigation, together with patient information and consent documents, were reviewed and approved by East of Scotland Research Ethics Service REC 2 (reference number 14/ES/0070), Tayside Medical Sciences Centre, Ninewells Hospital and Medical School, Dundee, UK. This investigation was conducted in accordance with ISO 14155:2011 and the ethical principles of the Declaration of Helsinki, as referenced in European Union (EU) Directive 2001/20/EC. It complied with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) and applicable regulatory requirements.

Consent for Publication

Not applicable.

Availability of Data and Material

The data that support the findings of this study are available from Reckitt Benckiser Healthcare Ltd., UK but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Reckitt Benckiser Healthcare Ltd., UK.

Competing Interests

GK, CB and NS are full-time employees of Reckitt Benckiser Healthcare Ltd., UK. MH-B is a full-time employee of the University of Salford, Manchester, UK.

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Authors Contributions

All authors contributed equally to the conception and development of this manuscript, critically reviewed the drafts and approved the final content, and were wholly accountable for its content.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

ABS: Acrylonitrile butadiene styrene;
ADE: Adverse device event;
AE: Adverse event;
CI: Confidence interval;
IITS: Investigator Ingrowing Toenail Severity;
ITT: Intention to treat;
SADE: Serious adverse device event;
SAE: Serious adverse event;
SD: Standard deviation;
SPI: Subject Pain Intensity;
UK: United Kingdom