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Introduction

Pin-site infections are a common problem during circular frame treatment, occurring in at least 30% of patients.[1] They are an important cause of morbidity, lead to antibiotic use, and increase the cost of treatment. Patients with pin-site infections suffer pain and loss of function which can impair their rehabilitation until the infection is resolved. This in itself may have long term consequences and, if left untreated, pin-site infections can cause more significant problems such as osteomyelitis or rarely septicaemia.[2] Current pin-site care practice commonly involves relieving skin tension around pin and wire insertion points, cleaning pin-sites on a regular basis and leaving pin-site crusts undisturbed [3]. Though various pin-site care regimes have been developed in an attempt to minimise problems with infection, practice remains varied and little strong evidence to support different approaches exists. This situation lead to the development of a consensus statement on pin-site care by a group from the Royal College of Nursing based on audit of current practice.[4] One finding from the work was that 90% of respondents agreed based upon their experience, that the use of emollients during pin-site care appeared beneficial. Given however the lack of evidence in this regard, it was suggested that a randomised trial should be conducted.

One aspect of interest in pin-site care is the effect of skin pH and hydration on host defence. Basic science evidence suggests that maintenance of these factors is important in the skins ability to resist infection.[5] Though it seems likely that the use of different products for pin-site care might affect skin pH and Hydration, the true effect is unknown. Similarly, the influence of these factors on rates of pin-site infection in patients treated with circular frames has not been determined. We therefore conducted a study to investigate the effect of using an emollient based pin-site care regime in comparison with one using alcohol based cleaning agents. This study received funding from both Smith & Nephew and Dermal Laboratories.

Aims

The primary aim of this study was to compare pin-site infection rates in patients with circular frames for tibia fractures using emollient or alcoholic skin preparation for weekly pin-site care. The null hypothesis was that no difference would be apparent. Secondary aims were to investigate the effect of using these different preparations on skin pH and hydration and to determine if any specific factors, including skin pH, hydration and histological characteristics, were associated with increased risk of infection.

Methods

Trial design and participants

A prospective, parallel, randomised controlled trial was undertaken with 1:1 allocation of participants to the two treatment arms. This trial was designed according to CONSORT guidelines. Ethical approval was gained from the Research Ethics Committee and the trial was registered on the European Database for Randomised Controlled Trials (2014-002223-10).

Adult patients (aged 16 or above) with acute tibial fractures in whom circular frame treatment had been selected as definitive treatment were included. These patients were recruited from two large tertiary hospitals in the United Kingdom offering a circular frame service between September 2015 and June 2017. Patients were excluded if they suffered dementia or cognitive impairment, had known sensitivities to the trial medication, were felt unable to follow pin-site care regimens for any reason or were involved in another clinical trial investigating a medicinal product within the previous four weeks. Patients were supplied with written information regarding the trial and consented for inclusion by a member of the team not providing clinical care.

Interventions

Patients were randomly allocated to two treatment groups: one receiving weekly pin-site using 0.5% chlorhexidine skin preparation (CHX) and the other using Dermol 500 emollient skin preparation (DML). Both groups were instructed to perform pin-site care once weekly in an otherwise identical manner as detailed in figure 1. Patients were specifically educated regarding pin-site care prior to discharge from hospital by a member of the nursing staff. A pin-site care pack was issued to each patient along with written instructions. Pin-site care was subsequently carried out either by the patient themselves, a member of the clinic or ward nursing staff or a district nurse, dependent on the situation, according to these instructions. A letter was sent to the patients family doctor to inform them that their patient had been enrolled in the trial and asking for the trial team to be informed if pin-site infections were diagnosed in the community.

Outcomes

The primary outcome measure was the rate of pin-site infection. Pin-site infection was diagnosed clinically by the clinical team caring for the patients and graded according to Clint et al. (Table 1). This system was chosen as it is validated and has demonstrated good inter- and intra-observer agreement[10].

Data collection

The schedule of routine data collection for the study is detailed in table 2. Information on baseline characteristics including demographics, co-morbidities, medications and injury details were recorded by the research team before surgery. Immediately after surgery, the grade of open fracture was recorded, classified according to Gustilio and Anderson, along with the number of half-pins and wires used in the frame.[6]

Skin pH (Courage-Khazaka PH-905 WL) and hydration (Courage-Khazaka CM-825 WL) were recorded immediately pre-op and every 6 weeks using commercially available devices for that purpose. Pre-operative measurements were recorded where possible from both the injured and uninjured leg. Measurements were taken from the least injured area of skin as judged clinically; a similar site was

used on non-injured leg. Where both legs were injured, skin on the thigh was used. At follow-up, measurements were taken from the anterior third of the tibia, and when infections were present, as close to the effected pin site as possible. Trial equipment was maintained and regularly calibrated according to the manufacturer's instructions.

During surgery, a 4mm punch biopsy (Meditech Systems Ltd, Dorset, UK) of skin was taken 10cm below the tibial joint line for histological analysis. The samples were stored at room temperature in 10% formalin and transferred to the laboratory. At analysis, specimens were embedded in a paraffin block and a microtome used to create 5µm slices. These were examined to record dermal and epidermal thickness as well as the capillary, macrophage and T-cell count per high powered field. The trial histopathologist was blinded to the treatment arm for each sample.

Following discharge, patients were interviewed by the trial team at each follow-up visit. Pin-sites were assessed for signs of infection and these graded. Skin pH and hydration measurements were taken as detailed above. Patients were interviewed to record pin-site care compliance and any episodes of infection that had been treated in the community. Changes in health status and medications used, protocol deviations and adverse events were also recorded. Trial completion was defined as occurring at 30 days post frame removal.

Randomisation

Simple randomization was undertaken, using a purpose built secure online platform, to allocate patients to treatment groups. This employed the Mersenne Twister algorithm (Robert G. Brown, Duke University Physics Department, 2019).[7] The system was tested through 1000 cycles and approved by the trial statistician as suitable for our trial randomization.

Statistical Analysis and Sample Size

A sample size calculation was undertaken using a 20% difference in the incidence of pin-site infection between groups as the threshold for clinical significance. Alpha (statistical significance) was set at 5% and beta (power) at 80%. Assuming a pin-site infection rate of 25%, based on data from the Cochrane review, it was calculated that 59 patients per group would be required required.[8]

The baseline characteristics between group (CHX and DML) are presented as mean (sd) or n (%). A chi-squared test was used to compare categorical variables between groups. Quantitative variables were compared using the Student's t-test, Mann Whitney-U or Kruskal-Wallis tests as appropriate to data type and distribution. Statistical significance was assumed at the $p < 0.05$ level.

Statistical analysis was undertaken using SPSS computer software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Results

Between September 2015 and June 2017, a total of 235 patients were screened for recruitment into the trial (Figure 2), 118 were subsequently enrolled. Two patients were withdrawn early because their treatment plans were changed, and they did not receive a circular frame. They were excluded from analysis, as they had no pin-site data to collect. This left 116 patients to follow-up, of which 59 received CHX treatment and 57 received DML treatment. There was no difference in patient demographic characteristics between CHX and DML groups as shown in table 3. No patients were lost to follow-up. There were 13 patients without skin samples due to this step being overlooked by the operating surgeon. No samples were lost during the trial.

The incidence of at least one bad or ugly pinsite infection was 41% in the CHX group, and 44% in the DML group (p=0729). Separating out the grade of pinsite infection into 'no infection', 'good', 'bad' and 'ugly' revealed a lower percentage of ugly pinsite infections in the DML group (9%) compared to CHX group (14%), although no significant difference was shown (Figure 3, p=0.743).

There was no difference found between the number of infections in each treatment group, with a mean average of 2.1 (SD 3.9) infections for CHX and 2.4 (SD 3.1) infections for DML (p=0.724). The location of pinsite infections was distributed to 25% in the proximal third, 33% in the middle third and 42% in the distal third of the tibia. Skin pH and hydration showed no difference at the start of the trial between readings for the injured and uninjured legs. This was used as a baseline measure.

There were a total of 66 patients with pinsite infections (57%). The mean average frame duration until a first time pinsite infection was 79 days (range 10 – 205 days). Table 4 shows that there were no statistically significant differences for age, gender, ethnicity, all co-morbidities, grade of open fracture, number of fixation elements used, smoking, alcohol consumption and daily moisturisers. There was no correlation between pinsite infection and the baseline pH (p=0.142) or hydration (p=0.546) of the skin. Figure 4 shows that frame duration had no correlation with incidence of pinsite infection.

From the histopathology specimens, it was noted that there was a significant association with the number of capillaries in the skin and pinsite infections (p=0.017). The epidermal and dermal thickness had no significant effect on pinsite infections, nor did the number of T-cells or macrophages seen per high powered field.

We found that four patients in the CHX group had sensitivities to their treatment resulting in skin irritation, itching and blistering in one case. Three had their treatments changed to pinsite care with cooled boiled water and one had treatment changed to DML which resolved the irritation. No sensitivities were seen in the DML group. The mean average compliance with all pinsite care regimens was 78%, with approximately half of patients fully compliant.

Conclusion

There was no statistical difference in the incidence of pinsite infection of any degree between CHX and DML treatment groups. This was the case when comparing each category of infection, and also when combining 'no infection' and 'good' for comparison with 'bad' combined with 'ugly'. Age, gender and comorbidities also did not affect which patients experienced a pinsite infection. This included diabetes, smoking, alcohol intake and steroid treatment. There was an incidence of 7% sensitivity to treatment in the CHX group compared to no sensitivity in the DML group. DML does contain chlorhexidine but in a lower concentration which seems to be less irritating to certain skin types. The baseline pH and hydration of the skin had no significant association with the incidence of pinsite infection. There was however a general trend to more acidic skin compared to baseline measurements

when pinsite infections were ‘bad’ or ‘ugly’. Similarly, the hydration also tended to increase from baseline when pinsite infections were ‘bad’ or ‘ugly’.

Limitations

There are several limitations to our study. There may be a small difference between treatment groups that we were unable to detect due to our sample size calculations for identifying a larger difference. This would lead our study to be underpowered, however we agreed that a difference of 20% between treatment groups would be the threshold for a clinically significant difference that would change practice. The surgeons and patients in this trial could not be blinded to the treatment arms because both CHX and DML are distinctively different and their treatment started whilst they were still inpatients. The surge in recruitment was unprecedented and as such we were unable to recruit all eligible patients. Only five patients from the entire screening log expressed that they did not want to take part in the research study. This is an important aspect that should be recognized when planning future research studies so that resources and funding can match recruitment. There were several occasions where the pH and Hydration probes needed to be re-calibrated via the manufacturer that led to gaps in data collection. There were no patients lost to follow-up. Several patients withdrew early from the trial and their reasons were mainly due to social issues. Study doctors who were well informed on the scoring system, recorded the pinsite infections. Even so, there may have been an observer bias to underestimate or overestimate the degree of infection. Compliance with study medication was checked verbally during follow-up clinics, but this aspect was very difficult to be certain about in some patients who had poor compliance in other aspects of their healthcare. This was a pragmatic trial that did not dictate how circular frames should be applied or which constructs should be used. The ratio of wires to half pins was left to the surgeon’s discretion. This may have introduced a bias between different methods of wire placement and skin handling. Skin samples were stored at room temperature in formalin until they could be batch processed. It is possible that some of the samples could have degraded whilst in storage, or that the thickness of the epidermis and dermis may have changed.

Discussion

There are a number of classification systems available for pinsite infection[9-13], however we believe that the classification system we used was appropriate. It is simple, clinically relevant and applicable with high inter-observer reliability[10]. We believe that pinsite inflammation and pinsite infection are two separate entities, but can co-exist. This may have acted as a bias when trying to interpret the results.

In order to track pinsite infections, we developed a simple labeling system for pinsites that could be used to map the pinsite details amongst different observers during each clinic visit. Rings were labeled alphabetically from proximal to distal, and pinsites were numbered according to the number of holes in the frame from the midline or master tab. A positive number represented a medial hole and negative number represented a lateral hole. The pinsites were also classed as proximal, middle or distal on the tibia and if there was any doubt then a free text comment could be recorded on the case report forms to help identify. Patients were also asked whether their infection was new or ongoing since their last clinic visit.

As far as we are aware, our research is the first to explore the baseline qualities of the skin barrier in the field of pinsite infections. The number of capillaries per high powered field was the only characteristic of skin that predisposed patients to pinsite infections. As this was one of our secondary objectives, the sample size was not set to measure its significance. We are intrigued by this finding and currently hypothesize that having more capillaries in the skin may increase the amount of inflammation and irritation around a pinsite, thereby increasing the likelihood of an infection occurring. The inflammatory phase may open the door to infection by providing an area of cellular breakdown that bacteria could then hijack. A new study to verify this finding would be useful.

Numerous techniques to of pinsite care have been published, but comparisons between studies have been difficult due to differences in study methods[14-24]. As a consequence, there is no widely accepted standard pinsite care regimen[1]. Chlorhexidine is a common agent used for pinsite care as it has been shown to reduce the pinsite colonization of Staphylococcus epidermidis and Staphylococcus aureus - the two most common organisms responsible for pinsite infection[25]. The dermol pinsite care regimen performed equally well compared to standard chlorhexidine treatment, but with less reported sensitivities.

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Figure 1 – Pin-site care instructions

1. Wash hands thoroughly.
2. Slide bungs or clips away and remove dressings.
3. Take a shower if you wish before the pin sites are cleaned.
4. In a clean bowl, place non-woven gauze / mouth sponge appropriate to the number of pin-sites
    a. For DML group: Pour over sterile water (can be cooled boiled water from a kettle) then pump the DML 8-10 times using clean hands to massage the DML and water into the gauze to form a foamy white substance. Use one swab / sponge per pin-site, remove excess solution and clean the pin-site.
    b. For CHX group: Pour CHX solution into bowl. Use one swab / sponge per pin-site, remove excess solution and clean the pin-site.
5. Do not remove crusts when cleaning unless loose.
6. Cut a piece of dressing and apply the clip or bung to hold the dressing in place.

Table 1: Grading system for assessing pinsite infections (Clint et al., 2010)

Grade	Erythema	Pain	Discharge
Good	None or minimal (less than diameter of pin)	None	None or minimal serous ooze (not requiring dressing changes)
Bad	Moderate (greater than pin diameter)	On palpation or percussion of pin	Serous discharge requiring dressing changes
Ugly	Severe (extending away from pinsite)	At rest	Heavy discharge or frank pus

Table 2: Patient investigations performed at each visit

	Pre-op on ward	In theatre	Subsequent clinic visits for duration of circular frame treatment
Timeline	-3 day to -1 day	0 day	+3 day until frame off
Consent into study	Yes		
Randomization		Yes	
Skin pH, hydration	Yes		Yes
Skin biopsy		Yes	
Record pinsite infection incidence and grade			Yes

Table 3: Patient demographics in each group

		CHX (n=59)		DML (n=57)	
		n	%	n	%
Gender	Female	20	34%	23	40%
	Male	39	66%	34	60%
Leg Receiving Frame	Left	29	49%	22	39%
	Right	30	51%	35	61%
Gustillo Grade of open fracture	0 - closed injury	45	76%	44	77%
	1 - low energy <1cm wound	0	0%	2	4%
	2 - low energy 1 - 10cm wound	0	0%	1	2%
	3a - high energy but wound	4	7%	3	5%
	3b - high energy, wound	9	15%	7	12%
	3c - high energy, contaminated,	1	2%	0	0%
Temporary ExFix	No	27	46%	30	53%
	Yes	32	54%	27	47%
Use daily moisturisers	No	48	81%	44	77%
	Yes	11	19%	13	23%
Diabetes	No	58	98%	54	95%
	Yes	1	2%	3	5%
Smoker	No	48	81%	43	75%
	Yes	11	19%	14	25%
Malignancy	No	59	100%	57	100%
Immunosuppression	No	59	100%	56	98%
	Yes	0	0%	1	2%
Active infection	No	59	100%	57	100%
Long term steroids	No	58	98%	55	96%
	Yes	1	2%	2	4%
Eczema	No	57	97%	56	98%
	Yes	2	3%	1	2%
Psoriasis	No	59	100%	55	96%
	Yes	0	0%	2	4%
Chronic Renal Failure on	No	59	100%	57	100%
Ethnicity	Asian or Asian British	3	5%	2	4%
	Black or Black British	1	2%	0	0%
	White	3	5%	7	12%
	White & Black Caribbean	1	2%	0	0%
	White British	49	83%	48	84%
	White Other	1	2%	0	0%
	Not stated	1	2%	0	0%
Health Status	Missing	1	2%	0	0%
	Fit and well	34	58%	39	68%
	Has comorbidities	24	41%	18	32%

Table 4: Pinsite infection by characteristics

	Pinsite infection		p-value
	No	Yes	
Grade of fracture			0.242
0 - closed injury	41 (46%)	48 (54%)	
1, 2 or 3 open fracture	9 (33%)	18 (67%)	
Smoker			0.577
No	38 (42%)	53 (58%)	
Yes	12 (48%)	13 (52%)	
T Cells	19.57 (10.03)	21.13 (8.82)	0.405
Capillaries	15.37 (4.36)	17.35 (3.89)	0.017
Epidermis	0.08 (0.04)	0.08 (0.04)	0.326
Dermis	2.33 (0.62)	2.20 (0.59)	0.298
Macrophages	17.02 (6.05)	17.84 (6.30)	0.505
Number of fixation elements (wires and half pins)	9.12 (2.74)	9.24 (2.35)	0.802
Skin pH	4.56	4.83	0.142
Skin Hydration	22	23	0.546
Skin treatment			0.831
Chlorhexidine	26	33	
Dermol	24	33	

Figure 2 – Consort 2010 Flow Diagram

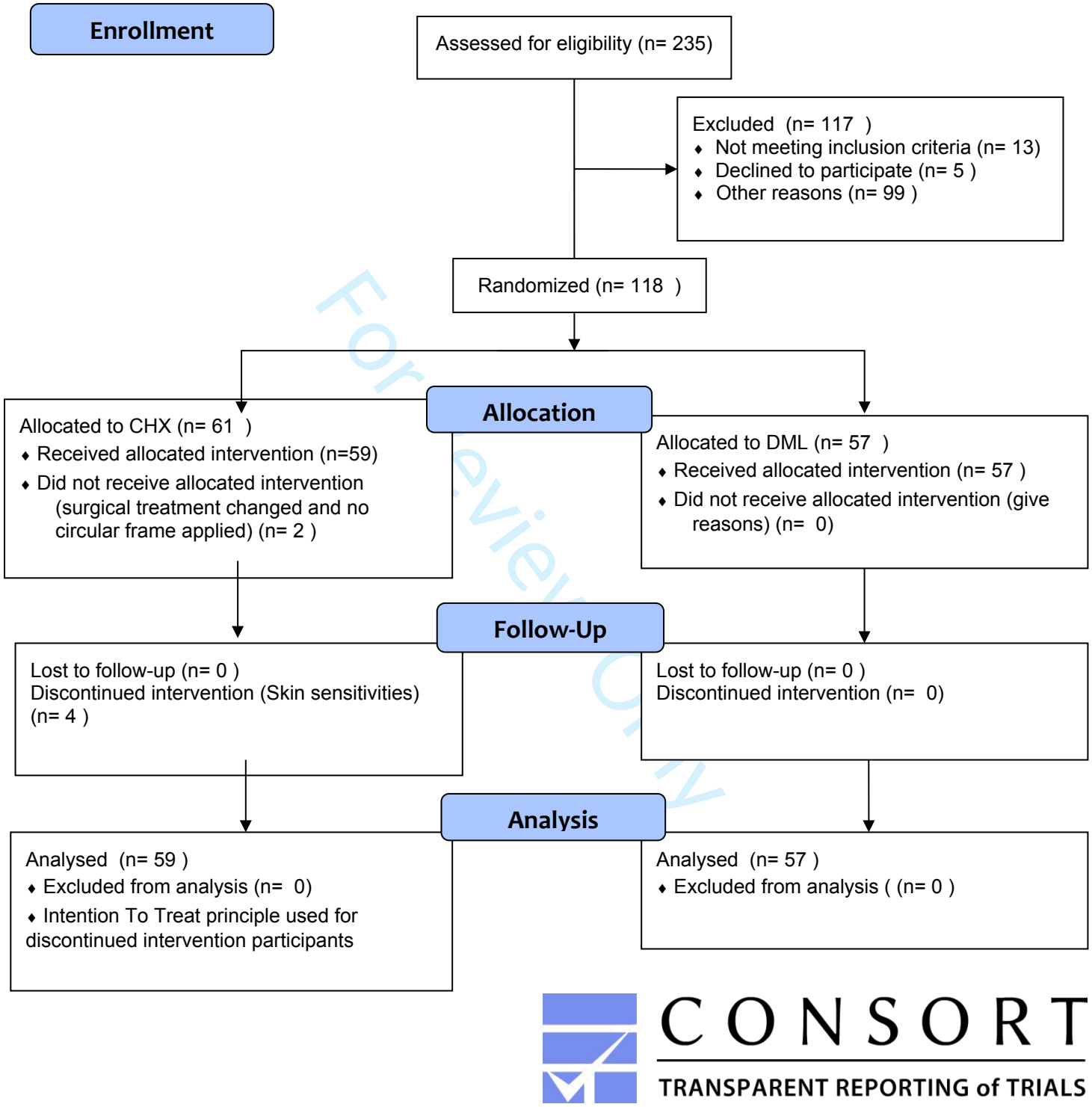

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Figure 3: Worst grade of pinsite infection during treatment (p = 0.743)

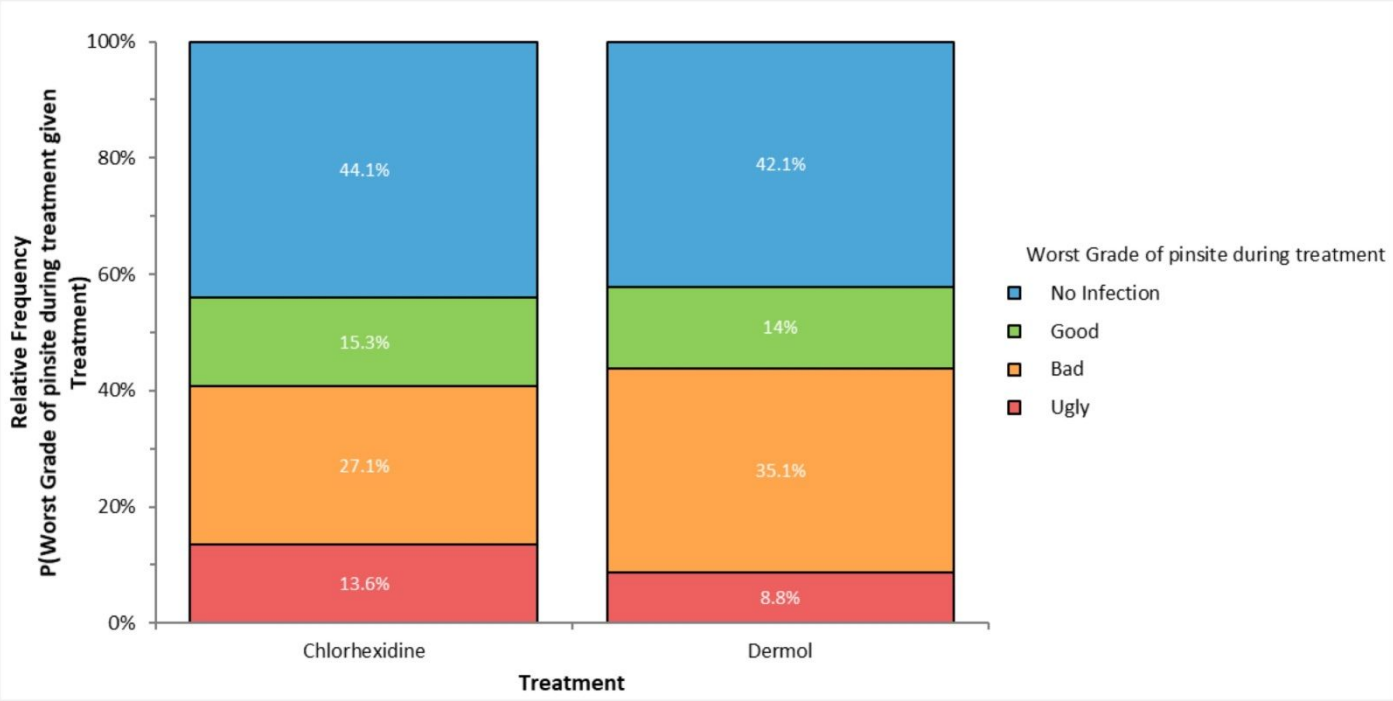

Figure 4: Correlation between incidence of new pinsite infections and frame duration (Correlation = 0.0169, p=0.857)