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Clinical trial

Natural coniferous resin salve used to treat complicated surgical wounds: pilot clinical trial on healing and costs

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Abstract

Resin is a natural product of coniferous trees. Salves manufactured from spruce resin (*Picea abies*) have been used for centuries to treat wounds and skin infections. We report a pilot clinical trial designed to investigate healing rates, factors that contribute to delayed wound healing, cost-effectiveness and incidence of allergic reactions when resin salve is used to treat complicated surgical wounds. The trial involved 23 patients in whom wound healing after surgery was delayed. These patients were assigned to resin salve treatment. The primary outcome measure was the number of days to complete wound healing. Se-condary objectives included an assessment of factors contributing to delayed wound healing, an estimation of associated costs and an investigation into the occurrence of allergic reactions related to resin salve therapy. The study achieved a healing rate of 100%. The mean ± SD healing time was 43 ± 24 d. The mean ± SD wound size (length × width × depth) was (29 ± 19) × (12 ± 7) × (4 ± 3) mm. Wound size, use of corticosteroids or other immunosuppressants and immobilization were statistically significant ($P < 0.05$) contributors to delayed wound healing and impaired re-epithelialization. The total mean ± SD costs of the resin salve treatment were €45.0 ± 26.0 per patient during the entire treatment period and €1.2 ± 0.5 per treatment day. The rate of allergic reactions was 0%. The results of this pilot trial indicate that complicated surgical wounds may be treated successfully with resin salve. The treatment method is clinically effective and cost-effective, and the rate of allergic reactions is low.

Introduction

Resin is a natural product of coniferous trees. In the Nordic countries, salve prepared from the resin of the Norway spruce (*Picea abies*) has been used for centuries to treat skin wounds, ulcers and skin infections.[1–4]

Wound healing may be impeded by any of several obstacles, including advanced age, infections, immobilization, ischemia, malnutrition, smoking, hyperglycemia, anemia, certain chronic diseases (e.g. diabetes, cancer, hepatic or renal failure) and the use of certain drugs (e.g. corticosteroids and other immunosuppressive drugs).[5,6] From a surgical perspective, infection of the surgical site contributes markedly to delayed wound healing.[7–9] Recent observations have shown that spruce resin exhibits strong antimicrobial activity against certain strains of bacteria and fungi that typically colonize wounds, cause infections and impede wound healing. Both *in vitro* and *in vivo* studies have shown that resin salve has significant antibacterial activity against pathogenic Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* species (VRE). The antifungal effect of the resin is exerted against the common dermatophytes of the skin, scalp and nails. Of the dermatophytes, *Trichophyton rubrum*, *Trichophyton tonsurans* and *Trichophyton mentagrophytes* have thus far been shown to be sensitive to the resin.[4,10–12] In the setting of a randomized, controlled clinical trial, resin salve proved to be more effective than sodium carboxymethylcellulose hydrocolloid polymer with or without ionic silver (Aquacel® or Aquacel Ag®; ConvaTec Ltd, London, UK) in the treatment of severe pressure ulcers.[11]

The objective of this study was to investigate the healing rate and healing time of complicated surgical wounds.

In addition, factors contributing to delayed wound healing, cost-effectiveness and incidence of allergic reactions to resin salve therapy were studied.

Materials and methods

Study setting and patient population

This was a clinical trial involving 23 patients whose wounds had not healed by primary intent after surgery. Based on our earlier experience, we hypothesized that the resin salve treatment might promote and accelerate the healing of such complicated surgical wounds. The inclusion criterion was the presence of a complicated, open, chronic surgical wound that had not healed by routine outpatient measures by 2 weeks after elective surgery. Exclusion criteria included life expectancy of <3 months, and the presence of wounds caused by trauma surgery or wounds scheduled for skin transplantation.

The primary outcome measure was the number of days to complete wound healing (i.e. full re-epithelialization of the wound). Secondary objectives were to assess factors contributing to the delay in wound healing, to estimate the costs of resin salve therapy and to study the rate of allergic contact dermatitis. Safety and compliance were monitored during the study every 2 weeks as part of regular control procedures in place in the outpatient department. If symptoms of contact dermatitis appeared, resin salve treatment was immediately discontinued.

The study was approved by the administration of the Helsinki University Hospital and Rheumatism Foundation Hospital. Written informed consent was obtained from all patients.

The study population was aggregated from routine postoperative outpatient department controls at the Rheumatism Foundation Hospital (nine patients, 39%) and Jorvi Hospital (14 patients, 61%) between January 2007 and December 2010. Experts in wound care (AS, RT, HK and OK) diagnosed the presence of a chronic surgical wound that indicated a need for resin salve treatment. These authors also followed up the patients, recorded and documented the clinical data and laboratory findings, and assessed the final outcome. The resin salve treatment was carried out as part of home care without exception. Demographic and pretreatment data for the study patients are shown in Table 1.

Spruce resin and resin salve

Pure spruce resin was collected in the municipality of Kolari, Finland, from the trunks of full-grown Norway spruce trees (Fig. 1). Bark and other impurities were removed mechanically. The resin was then liquefied and purified by filtering. Brown-colored resin salve is composed of a 10% (w/w) mixture of purified Norway spruce resin in a standardized salve base. None of the components of the salve base have antibacterial properties.[12] The product is produced to Finnish Good Manufacturing Practices (GMP) standards, carries the European CE (Conformité Européenne) mark, and is available commercially from Finnish pharmacies (Abilar® 10% resin salve; Repolar Ltd, Espoo, Finland).

Table 1 Demographic and pretreatment data for study patients (n = 23)

Variable	
Male/female, *n* (%)	8 (35%)/15 (65%)
Age, years, mean ± SD (range)	49 ± 17 (16–82)
Wound size, mean ± SD (range)	
Length, mm	29 ± 19 (5–60)
Width, mm	12 ± 7 (4–30)
Depth, mm	4 ± 3 (1–10)
Area, mm^2	424 ± 425 (25–1500)
Wound localization, *n* (%)	
Lower limb	8 (35%)
Upper limb	3 (13%)
Trunk or head	12 (52%)
Previous local treatment, *n* (%)	11 (48%)
Use of corticosteroids, *n* (%)	3 (13%)
Other immunosuppressants, *n* (%)	4 (17%)
Current smoking, *n* (%)	2 (9%)
Diabetes, *n* (%)	2 (9%)
Immobilization[a], *n* (%)	4 (17%)

[a]Need for assistance in moving.
SD, standard deviation.

Figure 1 Norway spruce (*Picea abies*)

Resin salve treatment

Regular daily wound care practice, including daily showers and dressing changes, was maintained. Within this, resin salve was applied to the wound in a layer approximately 1 mm thick and covered with sterile cotton gauze (Tyke HealthCare Ltd, Ulvila, Finland). General instructions for proper wound care and detailed instructions regarding the implementation of resin salve therapy were given by AS, RT, HK or OK as part of outpatient department practice. Despite the positive microbial culture of some wounds, profuse secretion of purulent discharge was not observed and no surgical revision was required for wound necrosis or slough.

Clinical variables

In addition to demographic variables, factors potentially contributing to wound healing were recorded at the beginning of the study. These included: wound size before resin salve treatment (length × width × depth, mm); the presence of rheumatoid disease or diabetes; smoking; use of corticosteroids or other immunosuppressants; immobilization; the presence of wound infection confirmed by a positive microbial culture, and previous attempts to treat the wound with wound care products other than the resin salve. The area of the wound was measured and infection status and any signs of allergic reactions were assessed during outpatient department visits every 2 weeks.

Cost analysis

To assess the total costs and daily costs of resin salve treatment, an average treatment cost (mean ± SD) per patient was calculated and total costs were extrapolated for the whole study group. Costs are expressed in euros (€). Cost analysis was based on the consumer price of the Abilar® resin salve and the Tyke HealthCare cotton gauze as recorded by the University Pharmacy in Finland on April 1, 2011. The following variables were recorded: (i) wound size (mm^2); (ii) daily consumption of resin salve (g) extrapolated in relation to wound size (mm^2); (iii) wound healing time (d); (iv) number (*n*) of 20-g tubes of salve purchased during the treatment period per patient; (v) cost of the 20-g tube of salve (€), and (vi) cost of any accessory products required (gauze).

Statistical analyses

Data analyses and reporting were based on STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13] Qualitative data are expressed as frequencies and percentages and quantitative data as the mean ± SD. Continuous variables and proportions were compared using the Mann–Whitney non-parametric *U*-test or Student's *t*-test, as appropriate. In univariate and multivariate logistic regression analyses, healing time was regarded as the dependent variable and other covariates, either dichotomous or continuous, were used as regressors. The use of corticosteroids and use of other immunosuppressive drugs, and diabetes and smoking, were combined into composite regressors because their incidences were low (fewer than five cases each). There were no missing data or loss to follow-up. Differences with a *P*-value of <0.05 were considered statistically significant. Analyses were conducted using SPSS Version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Healing rate and time

The healing rate of the chronic, complicated surgical wounds was 100% (23/23 patients). The mean ± SD healing time was 43 ± 24 d (range: 10–87 d; median: 41 d) (Fig. 2). Healing times did not differ statistically significantly between males and females. Detailed results of healing times are shown in Table 2. Figures 3 and 4 show wounds in two patients before and after resin salve treatment.

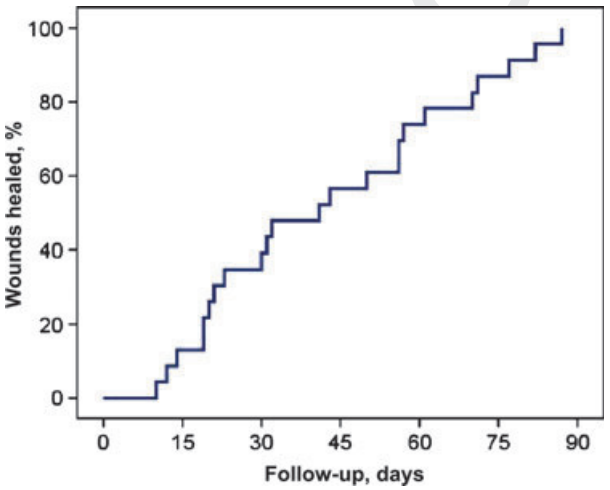

Figure 2 Healing over time of 23 chronic, complicated surgical wounds treated with resin salve

Table 2 Healing time of chronic complicated surgical wounds treated with resin salve (*n* = 23)

Variable	Healing time, d, mean ± SD	*P*-value
Whole study population (*n* = 23)	43 ± 24 (10–87)	0.238
Male (*n* = 8)	49 ± 23 (21–82)	
Female (*n* = 15)	39 ± 25 (10–87)	
Wound localization		
Lower extremity (*n* = 8)	56 ± 22 (19–87)	0.171
Upper extremity (*n* = 3)	41 ± 18 (30–61)	
Trunk or head (*n* = 12)	34 ± 25 (10–77)	
Previous local treatment		
Yes (*n* = 11)	50 ± 24 (19–82)	0.186
No (*n* = 12)	36 ± 24 (10–87)	
Wound infection		
Yes (*n* = 10)	47 ± 25 (19–82)	0.310
No (*n* = 13)	39 ± 24 (10–87)	
Diabetes or current smoking		
Yes (*n* = 3)	50 ± 16 (32–61)	0.438
No (*n* = 20)	42 ± 25 (10–87)	
Immobilization[a]		
Yes (*n* = 4)	76 ± 14 (56–87)	0.007
No (*n* = 19)	36 ± 20 (10–71)	
Use of corticosteroids or other immunosuppressants		
Yes (*n* = 5)	68 ± 15 (56–87)	0.01
No (*n* = 18)	36 ± 21 (10–77)	

[a]Need for assistance in moving.
SD, standard deviation.

LOW RESOLUTION COLOR FIG

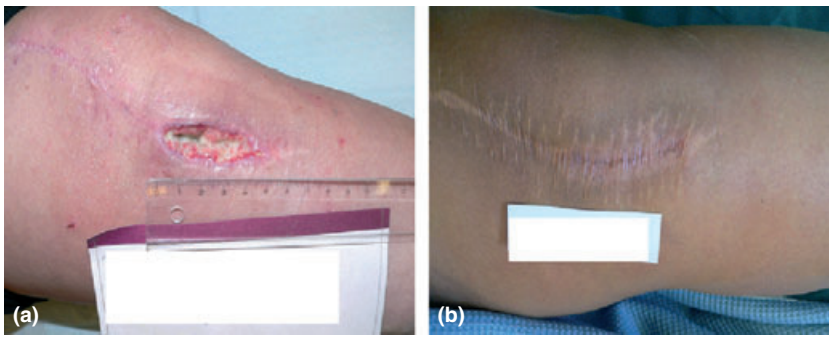

Figure 3 A 50-year-old woman on methotrexate and hydroxychloroquinine for rheumatoid arthritis underwent left knee arthrotomy. Postoperatively, she developed a chronic, complicated surgical wound which was treated successfully with the resin salve over 56 d. (a) Before and (b) after treatment

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LOW RESOLUTION COLOR FIG

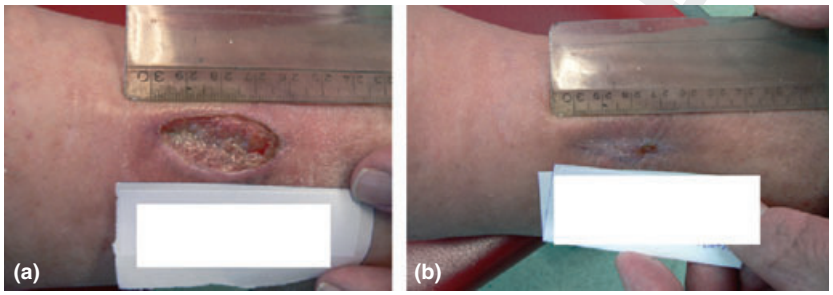

Figure 4 A 61-year-old man on methotrexate for psoriatic arthritis was treated with resin salve for 60 d for an open and complicated surgical wound that occurred after ankle joint arthrodesis. (a) Before and (b) after treatment

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Contributors to delayed wound healing

In univariate linear regression analysis, immobilization ($P = 0.001$), the use of corticosteroids or other immunosuppressants ($P = 0.004$), and wound size in terms of maximal length ($P = 0.016$) and depth ($P = 0.002$) were statistically significantly associated with prolonged wound healing (Table 3).

The multivariate linear regression model that showed the strongest correlation with wound healing time (adjusted $R^2 = 0.679$) included covariates of age, sex, wound size in terms of length, width, depth and wound area, use of corticosteroids or other immunosuppressants, smoking, presence of diabetes, immobilization and wound infection confirmed by positive bacterial culture. The covariates were entered into the multivariate regression model using a stepwise method. Statistically significant covariates for impaired wound healing were wound length ($P = 0.001$), use of corticosteroids or other immunosuppressants ($P = 0.014$) and immobilization ($P = 0.041$) (Table 3).

Costs

At the start of the study, the average wound area was 424 mm^2 and the amount of resin salve required for treatment was approximately 0.4 g/d. Thus, a 20-g tube of salve would last up to 50 d for a patient with a wound of this size at the start of treatment. Based on these extrapolations, the mean ± SD total cost of resin salve treatment for a mean treatment period of 43 d was €45.0 ± 26.0 (range: €22.0–102.0) per patient. The mean ± SD daily cost was €1.2 ± 0.5 (range: €0.5–2.2) per patient.

Allergic reactions and compliance

No adverse events or allergic reactions (i.e. contact dermatitis) related to resin salve therapy were reported during the study period. Compliance with the resin salve treatment was exceptionally good because there were no interruptions in the sample of patients recruited during the study.

Bacterial culture

Ten patients (43%) had a positive microbial culture. The bacterial strains were: *S. aureus* ($n = 5$, 50%); *Staphylococcus epidermidis* ($n = 1$, 10%); *Pasteurella multocida* ($n = 1$, 10%); a combination of *Streptococcus agalactiae* and *S. aureus* ($n = 1$, 10%); a combination of *Acinetobacter* and *Streptococcus* ($n = 1$, 10%), and a combination

Table 3 Effects of tested covariates on wound healing time in univariate and multivariate logistic regression analyses

Covariate	B	95% CI for B	R^2	*P*-value
Univariate analysis				
Immobilization[a]	39.71	17.78–61.64	0.375	0.001
Use of corticosteroids or other immunosuppressants	32.84	11.44–54.25	0.295	0.004
Wound size				
Depth	5.53	2.25–8.81	0.351	0.002
Length	0.64	0.13–1.15	0.221	0.016
Width	0.57	−1.10 to 2.23	−0.02	0.485
Area	0.02	−0.002 to 0.05	0.109	0.073
Age	0.52	−0.08 to 1.12	0.093	0.085
Sex	10.24	−11.86 to 32.35	−0.003	0.346
Infection[b]	10.52	−10.49 to 31.52	0.004	0.004
Diabetes or smoking	8.02	−23.72 to 39.75	−0.034	0.605
Multivariate analysis[c]				
Wound length	0.67	0.34–1.01	0.679	0.001
Use of corticosteroids or other immunosuppressants	24.07	5.50–42.64	0.679	0.014
Immobilization[a]	21.10	1.01–41.20	0.679	0.041

B, regression coefficient B; CI, confidence interval; R^2, adjusted coefficient of determination.
[a]Need for assistance in moving.
[b]Positive bacterial culture.
[c]Covariates tested in multivariate analysis: age; sex; wound size (i.e. length, width, depth and wound area); use of corticosteroids or other immunosuppressants; smoking; diabetes; immobilization, and wound infection.

of *S. aureus* and a Gram-negative rod (n = 1, 10%). Culture positivity or negativity did not affect wound healing time to a degree that was statistically significant.

Discussion

Our study indicates that the treatment of chronic complicated surgical wounds with resin salve is effective and feasible. Resin salve therapy seems to be well tolerated and treatment compliance is good. However, this was a clinical trial and, as such, does not give any evidence that resin salve would have improved the healing rate of the wounds with certainty. Randomized controlled trials are clearly required because the present findings are very encouraging.

The exact mechanism by which resin salve promotes healing and the identities of all active components that confer antibacterial and wound healing properties in resin and resin salve have not been fully elucidated. In wounds that are clinically markedly infected, it is probable that resin promotes wound healing because it has antimicrobial (i.e. both antibacterial and antifungal) properties. In culture experiments and electron microscopic studies, coniferous resin seems to destroy the bacterial cell wall and cell membrane.[12] In electrophysiological experiments, exposure to resin was found to decrease the cell membrane proton gradient in bacterial cells and this phenomenon was considered to be associated with a disruption of proton transport in the membrane-bound ATPase, resulting in the uncoupling of oxidative phosphorylation. Subsequently, the cell metabolism ceases and the energy supply is lost. In electron microscopy, the cell walls are thickened and the cells aggregated and, finally, degraded when bacteria are exposed to resin.[12]

The lignans that dissolve from the resin into water probably contribute significantly to wound healing and represent a biologically active component of resin salve. Lignans have antioxidative properties which change, through microbial metabolism and possibly other mechanisms, into components that, in their biological environment and through the impact of bacterial effects, become hormone-like.[14]

Previous studies have shown that the healing time of complicated and chronic surgical wounds varies widely and wound closure may take up to 500 d.[15] Our results in terms of wound closure time are in line with earlier findings or may be slightly shorter.[16] Although the risk factors for impaired wound healing, such as immobilization and the use of corticosteroids or other immunosuppressants, contributed negatively to wound healing in our study, all wounds did heal gradually when resin salve was applied. It is thus clear that resin salve treatment does not impede the wound healing process.

Infection contributes to impaired wound recovery and re-epithelialization.[7,8] Interestingly, the presence of a wound infection verified by positive bacterial culture

(43%, 10/23) had no marked influence on overall wound healing time in the present study. Although a positive bacterial culture, together with clinical signs of infection, is indisputable evidence for postoperative wound infection, a positive bacterial culture did not imply any significant deterioration in wound healing in this series. This may be explained by the antimicrobial properties of the resin salve, which have been clearly documented: resin is strongly antimicrobial against a wide range of Gram-positive and -negative bacteria, as well as against dermatophytes. Therefore, observations of accelerated wound healing regardless of positive bacterial culture may be based on the resin's capability to disinfect a wound by dispersing microbial biofilm from the wound cavity.[10–12] By contrast, in some cases, a positive bacterial culture probably indicated contamination from the patient's normal microbial flora rather than a true surgical wound infection. It is clear that, in such cases, the positive bacterial culture did not have any clinical significance or impact on wound healing (i.e. the microbes were just wound commensal flora). However, it is noteworthy that oral antibiotics were administered in our series only if the wound was clearly infected, and only when both clinical and laboratory-confirmed evidence of wound infection, including a body temperature >38 °C, redness or significant suppuration of the wound, and a C-reactive protein concentration of >40 mg/l, were available.

This study confirmed the classical and well-known risk factors for impaired wound healing: the use of corticosteroids or other immunosuppressive regimens, immobilization and wound size made statistically significant contributions to the impairment of wound healing. The best multivariate model to describe the duration of wound healing at an adjusted coefficient of determination (R^2) of 0.679 and a standardized regression coefficient (beta) of 0.532 indicated that an increase in wound length of approximately 2 mm prolongs average healing time by 1 d and that a chronic, complicated wound 3 cm in length should heal, on average, in 15 d. Although logistic regression models are frequently used in observational studies, the impact of an observed risk factor must be interpreted extremely carefully [i.e. as the regressor on the outcome (dependent variable)]. Patients differ not only in terms of the presence or absence of the risk factor being tested, but also in terms of numerous other patient-related factors, which can potentially contribute to outcome and are thus able to bias the results. By contrast, some of the most important reasons for using multivariate models are to control potential confounding factors, minimize the impact of these confounders on the outcome and, thus, enable the emergence of actual risk factors.[17]

Estimating the costs incurred by wound care and conducting a reliable comparison of the costs of wound care products is a difficult enterprise.[16,18,19] There are approximately 300 topical wound care products on the market and consumer prices, packet sizes and daily usage vary markedly. In addition, recommendations and guidelines related to wound care are heterogeneous among hospitals and specialist wound care units.[20] Nevertheless, we attempted to estimate the costs of resin salve treatment of chronic, complicated surgical wounds and concluded that resin salve treatment is inexpensive and cost-effective in comparison with, for example, medical honey or sodium carboxymethylcellulose hydrocolloid polymer treatment, both of which are commonly used for wound care. Furthermore, the average wound healing time in our study was somewhat shorter than in earlier studies[15,16] and the current price of resin salve in Finland is only 10–20% of the consumer price of medical honey (Actilite®; Episil 6
Border®) or sodium carboxymethylcellulose hydrocolloid 7
polymer without or with ionic silver (Aquacel® or Aquacel Ag®; Duoderm Extra Thin®). A recent randomized 8
clinical trial by Ubbink *et al.*[16] compared the effectiveness and cost of occlusive dressings against those of gauze dressing for local wound care in surgical patients. The authors reported that the overall daily cost per patient was €7.48 in the occlusive dressings group and €3.98 in the gauze dressings group.[16] The overall daily cost of resin salve treatment was approximately €1.2 ± 0.5 per patient in the present study.

Resin allergy has been reported to occur at a prevalence of 1–3% in the general population.[21–23] This study included 23 patients treated with resin salve, among whom no allergic reactions occurred. An earlier study involving 21 patients in whom severe pressure ulcers were treated with resin salve for ≤6 months reported that only one patient dropped out because of severe allergic contact dermatitis.[11] It appears that the risk for allergic contact dermatitis is low, but the risk for resin sensitivity must be taken into account in nursing practice.

Although our follow-up was complete and no patients were lost to follow-up, the study has some limitations. It represents a non-randomized, uncontrolled pilot clinical trial, in which surgical patients were recruited from only two centers by four researchers. Thus, the study carries a risk for selection bias because patients were recruited into the study by the authors only, and not all patients from the two recruiting centers who would have fulfilled the entry criteria were recruited. Our results will require consolidation in a randomized controlled study setting in the future. In addition, we were unable to report patients' blood glucose and hemoglobin levels during the treatment period and this ignorance of these potential contributors to wound healing in this clinical trial is an obvious limitation. However, there are some obvious obstacles to patient recruitment, including the general lack of interest

in this type of non-conventional wound treatment. We hope that the good results documented in trials thus far will kindle an interest in the use of resin salve to cure difficult-to-treat, chronic, inflamed surgical wounds.

In conclusion, this study suggests that resin salve treatment is a clinically effective and cost-effective means of promoting the healing of chronic, complicated surgical wounds.

Acknowledgments

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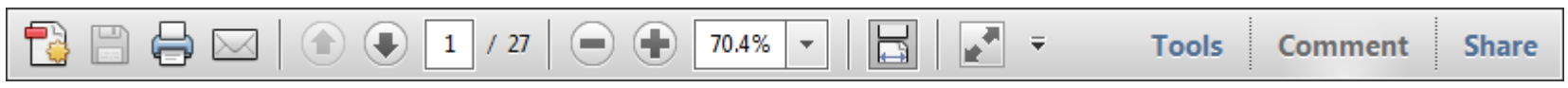
10	AUTHOR: insert full name of department, institution (include the town, country of the institution if it is not cited in the author affiliations) of RP.	
11	AUTHOR: Please check this page range for reference [19], [20] and [21005D.	
12	AUTHOR: Please check this page range is correct.	
13	AUTHOR: Please check this page range is correct.	
14	AUTHOR: Figure 3 has been saved at a low resolution of 233 dpi. Please resupply at 300 dpi. Check required artwork specifications at http://authorservices.wiley.com/submit_illust.asp?site=1	

15	**AUTHOR: Figure 4 has been saved at a low resolution of 265 dpi. Please resupply at 300 dpi. Check required artwork specifications at http://authorservices.wiley.com/submit_illust.asp?site=1**	

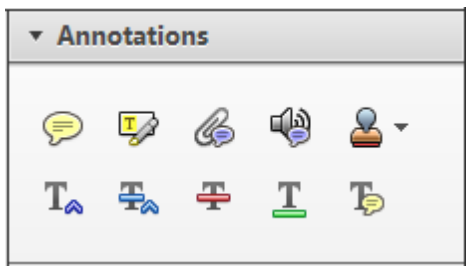
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 8.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: http://get.adobe.com/reader/

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

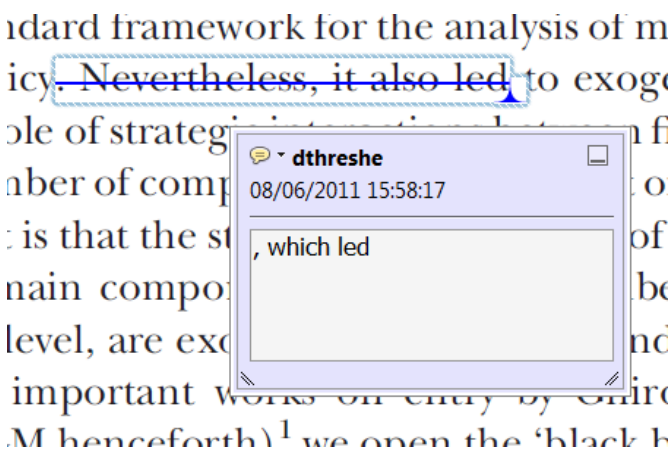


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

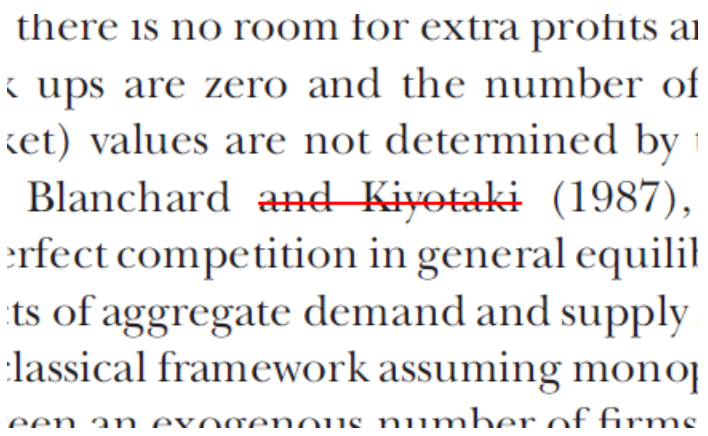


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

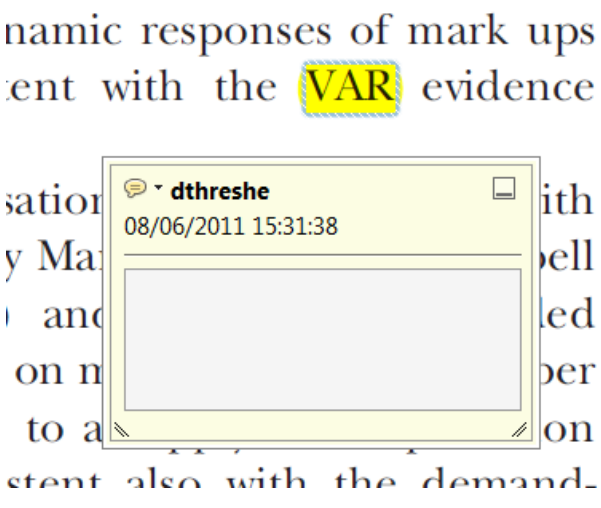


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.

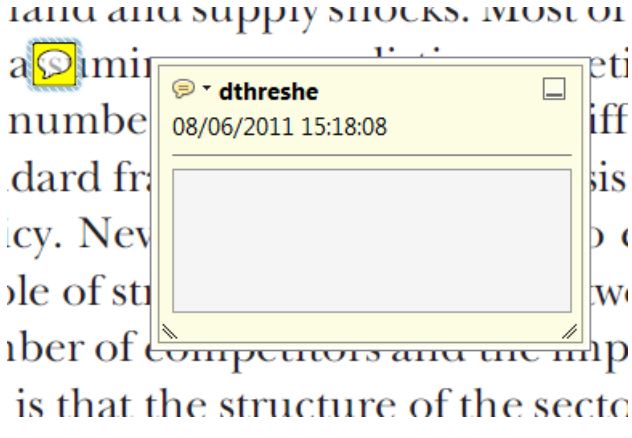


4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

How to use it

- Click on the Add sticky note icon in the Annotations section.
- Click at the point in the proof where the comment should be inserted.
- Type the comment into the yellow box that appears.



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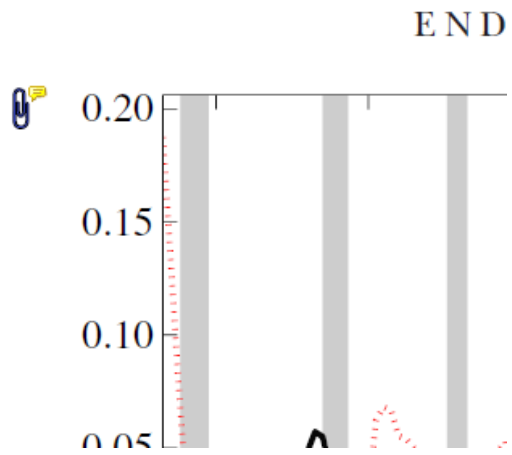
USING e-ANNOTATION TOOLS FOR ELECTRONIC PROOF CORRECTION

5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
- Select the colour and type of icon that will appear in the proof. Click OK.

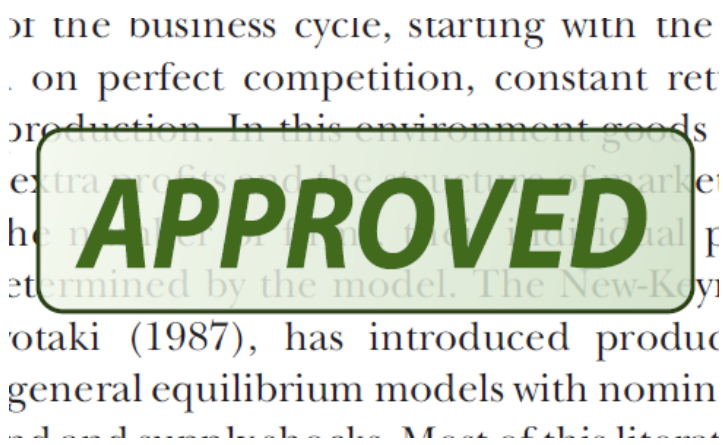


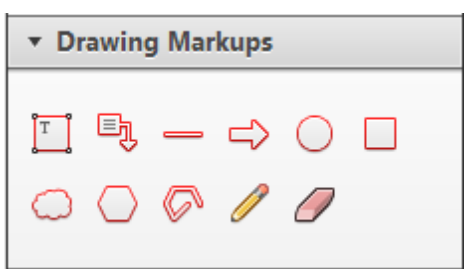
6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

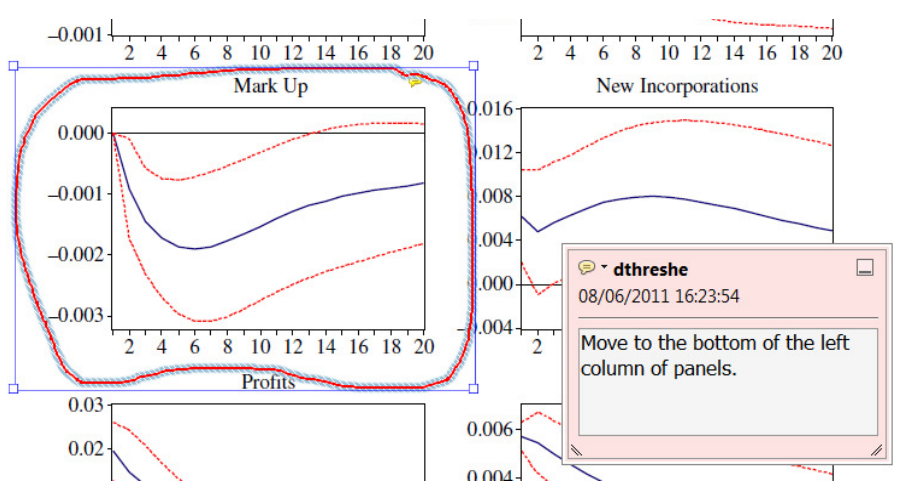
- Click on the Add stamp icon in the Annotations section.
- Select the stamp you want to use. (The Approved stamp is usually available directly in the menu that appears).
- Click on the proof where you'd like the stamp to appear. (Where a proof is to be approved as it is, this would normally be on the first page).





7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..



How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.

For further information on how to annotate proofs, click on the Help menu to reveal a list of further options: