An RCT on the effects of topical CGP on surgical wound appearance and residual scarring in bilateral total-knee arthroplasty patients

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**Objective:** To test the hypothesis that topically applied calcium glycerophosphate (CGP) would improve the appearance of the wound following bilateral knee replacement.

**Method:** Healthy patients, aged 45–75 years, scheduled for bilateral total-knee replacement surgery were recruited into the study. One knee was randomly assigned to the treatment group, while the contralateral knee was designated the control (standard care). Subjects were instructed to apply a preparation of 10% CGP in an aqueous lotion to the treated knee once daily for 42 days, starting at the third postoperative day. Functional sealing and cosmetic appearance of the incision were evaluated by two surgeons by direct examination of the patient and then by two experienced assessors from photographs. The investigators qualitatively scored the intensity and extent of erythema along the incision and over the entire knee, the appearance of visible oedema along the incision and over the knee, and the overall clinical impression of wound healing. All four assessors were blinded to the subjects’ allocation and the latter two assessors to the initial investigators’ assessments. Subjects were also followed up for an additional 46 weeks, giving a total study duration of 12 months.

**Results:** Twenty patients completed the study. Statistical analysis showed that both the area and intensity of erythema along the incision were significantly reduced in the treated vs untreated knee over the entire study period. The analysis further showed that treatment significantly reduced oedema, both along the incision and across the entire knee. The differences were most marked at the seventh postoperative day and diminished with time. No adverse effects were observed for any patient, in either treated or untreated knees.

**Conclusion:** These data demonstrate that postoperative application of 10% CGP could improve the appearance of the wound following total knee arthroplasty.

**Declaration of interest:** This study was supported by a grant from AkPharma Inc. Dr M.T. Weis has performed paid consultant work for AkPharma during past 10 years. No person or institution performing work on this study has any financial connection with AkPharma Inc., or any financial interest in the outcome of this study, or in the components used in this study.
upregulating expression of cell-cell adhesion proteins.26 Ultimately, these processes recruit tissue fibroblasts to repair, stimulate endothelial progenitor cells to vascularise, and stimulate keratinocytes to re-epithelialise the wound. The activity of the kinases is limited by phosphatases, which oppose kinases by removing phosphate groups from their protein or lipid targets, thus reversing their effect. Thus, the rate of healing is affected by the ratio of phosphorylated (kinase-mediated) to dephosphorylated (phosphatase-mediated) species.

Platelet lysates activate protein kinases,27,28 increasing fibroblast migration to the wound.29 While laser treatment, by generating heat, activates a pathway that ends with the inhibition of phosphatases,30–33 autologous platelet gels and laser treatment have been explored as a means of accelerating wound healing.34–37 and in cosmetic revision of surgical scars, with or without further surgery.2 Both are expensive and have yielded marginal results.38,39

As reviewed by Lansdown,11 calcium stimulates the kinases that are important in wound healing, while glycercophosphate inhibits phosphatases, including those involved in the response to epidermal growth factor.40,41 Thus, we speculated that, by simultaneously stimulating kinases and inhibiting phosphatases, glycercophosphate (CGP) would speed surgical wound healing, and perhaps improve long-term cosmetic effects. CGP is inexpensive (< $100 per knee for the 6-week course of therapy) and easy to apply.

CGP is commercially available as a dry granulate from a number of manufacturing sources. The formulation used in this study is not yet commercially available. The study sponsor has patents issued and has yielded marginal results.38,39

The primary endpoint of this trial was improvement of surgical wound appearance. Secondary outcomes were reduced visible erythema/inflammation, scar minimisation, reduced patient-reported scar-associated pain and sensitivity, as well as improved range of motion. Method

This study was undertaken jointly by the Rothman and Bacharach Institutes (surgery was performed at the Rothman Institute and rehabilitation at the Bacharach Institute). The Rothman Institute is affiliated with the department of orthopaedic surgery of Thomas Jefferson University School of Medicine. The Bacharach Institute is a licensed rehabilitation hospital. Potential participants were identified and enrolled sequentially from a pool of candidates consisting of all patients eligible for simultaneous bilateral knee replacement at the Rothman Institute.

Participants

Patients were considered eligible for inclusion if they were judged to be in otherwise excellent health, were scheduled for bilateral knee-replacement surgery and were aged between 45 and 75 years of age on the day of assessment. This age range was chosen to be consistent with that of the patient population eligible for bilateral TKA at the Rothman Institute.

Patients were excluded if they did not give written informed consent to participate, or if they were an employee or immediate family member of AkPharma Inc., an investigator or one of the site personnel. Additional exclusion criteria were:

- Pregnancy or breast feeding
- Known allergy or hypersensitivity to calcium or phosphorus supplements
- Diagnosis of type I or type II diabetes mellitus

Prior to initiation of the study, the proposed protocol, informed consent form and product information were approved by the Bacharach Institute for Rehabilitation Institutional Review Board. The protocol is registered as study NCT01264588.

Eligible patients were assigned, by 1:1 randomisation, to apply the study product formulation topically to either the left or right knee incision, with the contralateral knee incision serving as the control group. To ensure allocation concealment, the sponsor prepared blinded treatment kits containing 42 pre-measured doses of CGP preparation, application instructions, a treatment diary, and the subject’s randomisation assignment (right/left). The blinded kits were dispensed by the clinical research coordinator, in numerical sequence, to the participants, who were also in numerical sequence. Kits were prepared in blocks of four, each block comprising two designated ‘left’ and two designated ‘right’. This blinded the sponsor as to which patient received which kit, while the surgeon did not know whether a particular kit had been designated left or right. The assessments were conducted by a surgeon (one orthopaedic surgeon and one plastic surgeon) who were blinded as to the left/right assignment. The study sponsor had no part in evaluating the wounds.

Qualitative baseline assessments were made on the third day postoperatively (visit 2), prior to treatment and included patient gender, age and race.

Interventions

CGP was prepared as a 10% suspension (w/w) in an aqueous lotion base consisting of DL-lactic acid (1.95%), cellulose gum (2.5%), glycerin (1%), methylparaben (0.2%), and water (84.35%). The study sponsor prepared and supplied all treatment kits.

The Rothman Institute wound care guidelines (control group) were the standard care against which CGP treatment was measured. The standard was to clean the wound site with normal saline daily. As per the guidelines, the use of povidone-iodine (Betadine) on either wound was specifically avoided. Once the product was dry, both wounds could be covered with a sterile surgical pad (Combine ABD Pad; Dukal) held

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References

Outcomes
The primary outcome of improvement in the surgical wound appearance, and the following secondary outcome measures, were sequentially evaluated for the first postoperative year:
- Reduction of visible erythema/inflammation
- Scar minimisation or prevention
- Patient-reported pain and scar sensitivity
- Range of motion.

Functional sealing and cosmetic appearance of the wound were measured by qualitatively scoring the intensity and extent of erythema along the incision and over the entire knee, the appearance of visible oedema along the incision and over the knee, and the global impression of wound healing; that is, the overall appearance of sealing, oedema and erythema and general cosmetic appearance of the wound was judged. The side perceived as worse was assigned a score of 0, while the side perceived as better was assigned a value of 1–4, where 1 represents (least difference) and 4 (greatest difference), respectively; similar scoring systems have been used on TKA patients in previous studies. Tri and 4. If the two sides were indistinguishable, each side was assigned a score of 0.5. All scores were recorded as left knee vs right knee for each patient.

Participants were asked to rate the pain associated with the scar itself and to differentiate that pain from the overall pain of the TKA procedure. The pain evaluations were recorded using self-reported visual analog scale (VAS).

The clinical research coordinator in charge of the study took digital photographs, as objective measurements, at every postoperative visit, using a camera supplied by the sponsor. The photographs were coded with the patient number, with no indication as to the treated knee. An orthopaedic surgeon (independent of the one performing the TKA) and a plastic surgeon, blinded as to which knee was treated, evaluated the differences between left and right knees, both by direct examination of the patient and from the photographs. The photographs were examined additionally by two individuals experienced in evaluating the effect of pharmacological agents on skin, who were blinded as to the subject’s allocation, history and the investigator’s assessment of the knees. The scores of each evaluator received equal weight when tabulating and analysing results.

Statistical analysis
The tabulated scores for each patient were analysed by two-way (treatment, visit) analysis of variance, using the Bonferroni post-hoc test, as per the Prism 5.0b software package (GraphPad Software Inc.). In addition, each visit was analysed by the Wilcoxon matched pairs signed-rank test. Significance was taken as p<0.05. Our sample size of 20 subjects gave an 80% power to detect a medium to large effect size, for a two-sided test of significance at a critical level of p=0.05. All tests were against a two-sided alternative. Dropouts in this trial were sequentially replaced to maintain the power of the study.

Results
The first 15 patients enrolled in the study were supplied product in a squeeze bottle. Concordance was evaluated at 6 weeks postoperatively (visit 5) by weighing the unused product. It was determined that 11 of these 15 patients were non-concordant. The...
study was placed on hold while the product packaging was changed to unit-dose format, as detailed above. Subsequent patients were supplied only with unit-dose product; there was 100% concordance with the new dispensing format. All non-concordant patients were excluded from data analysis.

Of the 40 patients assessed for eligibility, 20 completed the study. Although the sample size was small, the gender (χ^2=1.643; p=0.20) and ethnic distribution (χ^2=0.3510; p=0.5535) of patients were not different from that expected by chance. The final patient population is described in Table 1 and the flow of participants through each stage of the trial is given in Fig 1.

Results indicated to be statistically significant (p<0.05) by ANOVA analysis were also considered significant by non-parametric analysis (Wilcoxon signed-rank test). The expert graders’ scores for all patients for erythema, oedema and global impression of wound healing are shown in Figs 3–5. As shown in Fig 3a,c, both the area and intensity of erythema along the incision were significantly reduced (scored higher) in the treated vs untreated knee (p=0.003).

The difference was greatest on day 7 (visit 3; Table 2) and diminished with time. By the 6 months, postoperatively (visit 8), the scar appearances of the treated and untreated knees were no longer distinguishable. While treatment significantly reduced (scored higher) the area (Fig 3b; p=0.002) and intensity (Fig 3d; p=0.003) of erythema over the entire knee, the effect was less visually obvious than that observed directly along the incision site.
The treated knees had significantly less oedema, both along the incision (Fig 4a; p < 0.0001) and across the entire knee (Fig 4b; p = 0.002). As with erythema, the effect was greatest on day 7, and diminished with time.

The global impression of wound healing was markedly and significantly better in the treated vs the untreated knee (Fig 5; p < 0.0001). As with the other outcomes, the effect diminished with time. At visits 3–9 the treated knees scored consistently higher than the untreated. However, at visit 9 (day 365) the difference between treated and untreated appeared to be increasing, rather than decreasing (0.556 ± 0.232, for standard care, vs 0.956 ± 0.233, for CGP treatment, and 0.450 ± 0.201, for standard care, vs 1.13 ± 0.32, for CGP treatment, for visits 8 and 9, respectively).

Patients were asked to evaluate pain at the site of incision using the VAS. Overall, these scores were low. The mean pre-treatment pain score (third post-operative day) was 1.78 ± 0.64mm for the treatment-designated knee vs 1.75 ± 0.63mm for the untreated knees (p = 0.867). By visit 3 (seventh day postoperatively; fourth day of treatment), pain recorded at the site of the incision had decreased to 0.88 ± 0.35mm in the treated vs 0.85 ± 0.40mm in the untreated knee (p = 0.867). At no time was there a significant difference in the pain scores between the treated and untreated knees. Overall, the mean pain score declined with time, so that by one year postoperatively no patient reported pain associated with the incision in either knee.

At visit 2, before treatment, the mean flexion was 66.0 ± 3.3° for the knee assigned to the treatment group and 71.0 ± 2.4° for the contralateral knee. These values were significantly different from each other (p = 0.046). As shown in Fig 6, by 6 weeks, the treated knee had gained 40.0 ± 3.5° of flexion, compared with 34.0 ± 3.2° for the contralateral knee (p = 0.02). By 6 months, there was no difference in flexion between treated and untreated knees.

At baseline, the mean extension was -4.6 ± 1.5° for the knee assigned to the treatment group and -4.4 ± 1.6° for the contralateral knee (p = 0.855). By 6 weeks, the mean extension of the treated knee had improved by 4.4 ± 1.6°, compared with 3.4 ± 1.8° for the untreated knee (Fig 6); although this difference was not significant (p = 0.07). By 6 months, and at one year, the extension of all knees, treated or untreated, was zero.

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**Table 1. Patient demographics (n=20)**

<table>
<thead>
<tr>
<th>Gender (n)</th>
<th>Male</th>
<th>Female</th>
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<table>
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<tr>
<th>Race (n)</th>
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<table>
<thead>
<tr>
<th>Age (years)</th>
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<th>Median</th>
<th>Mode</th>
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<tr>
<td></td>
<td>61.25</td>
<td>62</td>
<td>62</td>
<td>49–72</td>
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This suggests the intriguing possibility that late-stage healing may be affected by the gains in early stage healing, as has been suggested for burns. At no time postoperatively did CGP treatment affect pain associated with the incision; however, patients did not report high levels of incision-associated pain for either knee. The incision-associated pain was low, possibly due to concurrent postoperative analgesia. Regardless, CGP treatment did not appear to increase pain at the incision site.

The data suggest that CGP treatment may be associated with earlier gain in range of motion in the immediate 6-week postoperative period. The treated knees gained flexion earlier than the untreated knees, suggesting that the reduced erythema/oedema observed in the treated vs untreated knees facilitated recovery of range of motion. However, this result must be interpreted with caution. Prior to treatment, the knees assigned to the treatment group had a degree of flexion that was significantly worse than the contralateral knees. The gain in flexion may simply be an artefact attributable to the initial inequality. Despite this, at the very least, the data show that CGP treatment did not impair recovery of range of motion.

The usual confounding factors of an arthroplasty wound healing study, such as different surgical techniques, different implant devices and comorbidities, such as diabetes, were absent from these studies. Limiting the study to otherwise healthy patients having bilateral TKA narrowed the number of variables, and allows us to conclude that the differences observed between the treated and untreated knees are most likely the result of CGP therapy. While eliminating these variables does remove important confounding factors, it also limits the interpretation of the study. That is, the data demonstrate a treatment effect in otherwise healthy patients. Arguably, the probability of observing increased speed of wound healing is lowest in this patient population. The effect of CGP treatment in patients with chronic diseases is and remains unknown. The large treatment improvement patients having bilateral TKA narrowed the number of variables, and allows us to conclude that the differences observed between the treated and untreated knees are most likely the result of CGP therapy. While eliminating these variables does remove important confounding factors, it also limits the interpretation of the study. That is, the data demonstrate a treatment effect in otherwise healthy patients. Arguably, the probability of observing increased speed of wound healing is lowest in this patient population. The effect of CGP treatment in patients with chronic diseases is and remains unknown.

The objective of this study was to evaluate the efficacy of topical CGP in the overall healing and cosmetic appearance of surgical incisions. The results of this study demonstrate that topical CGP application might speed wound healing in TKA. The difference was particularly marked on the seventh day postoperatively, when better wound appearance was observed. The results of the present study suggest that even greater differences might be observed in the population with comorbidities, such as diabetes, that were not included in this study due to the exclusion of patients having bilateral TKA.

**Discussion**

The data suggest that CGP treatment may be associated with earlier gain in range of motion in the immediate 6-week postoperative period. The treated knees gained flexion earlier than the untreated knees, suggesting that the reduced erythema/oedema observed in the treated vs untreated knees facilitated recovery of range of motion. However, this result must be interpreted with caution. Prior to treatment, the knees assigned to the treatment group had a degree of flexion that was significantly worse than the contralateral knees. The gain in flexion may simply be an artefact attributable to the initial inequality. Despite this, at the very least, the data show that CGP treatment did not impair recovery of range of motion.

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**Table 2. Mean scores for area and intensity of erythema at postoperative day 7 (visit 3), after 4 days of CGP treatment**

<table>
<thead>
<tr>
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<th>Standard care</th>
<th>CGP treatment</th>
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<tr>
<td>Area of erythema along incision</td>
<td>0.385 ± 0.178</td>
<td>1.55 ± 0.24</td>
</tr>
<tr>
<td>Intensity of erythema along incision</td>
<td>0.300 ± 0.147</td>
<td>1.46 ± 0.23</td>
</tr>
<tr>
<td>Area of erythema over entire knee</td>
<td>0.250 ± 0.123</td>
<td>0.530 ± 0.131</td>
</tr>
<tr>
<td>Intensity of erythema over entire knee</td>
<td>0.200 ± 0.092</td>
<td>0.535 ± 0.129</td>
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*Fig 5. Global clinical impression of wound healing for all patients*  
*Fig 6. Improvement in range of motion between visit 2 (pre-treatment) and visit 5 (6 months)*
impair wound healing. Although it is well beyond the scope of this study, a future study of CGP in these patients is clearly warranted.

Although not an objective of this study, it would be of interest to discover whether CGP reduces the incidence/severity of keloid formation, particularly to those of African ancestry. The inclusion of only two persons of African ancestry does not permit us to address this important question.

The initial poor patient concordance illustrates the importance of dosage format. When dispensed in a squeeze bottle, patients had difficulty judging how much product to apply at each treatment. However, when the product was supplied in a unit-dose format, concordance (as evaluated by measuring unused product) was judged to be significantly better.

This study did not use the Vancouver Scar Scale (VSS) or Patient and Observer Scar Assessment Scale (POASS), as these scales are designed to minimise variability in assessing single scars on different patients, not similar scars on the same patient, evaluated side-by-side. Scar assessment tools are subjective measurements, whether the Likert scale used in this study, similar scales used in other TKA scar evaluation studies,26 the VSS or POASS. As this is a small trial performed at a single centre, all evaluations were performed by the same team, minimising rater variability as a source of error. Nevertheless, we realise that, by not using the VSS or POASS, it may be difficult to compare the results of this trial to other studies. Certainly, these more conventional systems, as well as colorimetric rating of erythema, should be used in a larger, multi-centre trial.

Therapies to improve wound healing have been pursued in both laboratory and clinical studies. Although rapid wound healing is associated with improved surgical outcomes, current standard care includes no agents, topical or systemic, that speed postoperative wound healing. As stated earlier, autologous platelet gels and laser treatment have yielded marginal or inconsistent results. Platelet-derived factors, laser therapy and CGP may act through a group of common effectors. Platelet lysates likely activate protein kinases,27,28 increasing fibroblast migration to the wound.29 CGP certainly supplies free calcium, activating both platelets and kinases. Laser treatment, by generating heat, appears to activate a pathway that ends with the inhibition of phosphatases,30–32 and glycerophosphate is a general phosphatase inhibitor.40,41

Proper preparation of autologous platelet gels is difficult, expensive, and exacting.38 Successful laser treatment is expensive, and requires multiple treatments.32 In contrast, CGP is inexpensive (< $100 per knee for the 6-week course of therapy) and easy to apply.

Conclusion

The present study shows that CGP promotes surgical wound healing in otherwise healthy subjects undergoing TKA, and suggests that it may improve the long-term cosmetic appearance of the surgical scar. These properties suggest that CGP merits further investigation in a broader patient population, as well as for other surgical procedures.