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Homeopathic arnica therapy in patients receiving knee surgery: Results of three randomised double-blind trials[☆]

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KEYWORDS

Randomised clinical trial;
Homoeopathy;
Arnica;
Arthroscopy;
Artificial knee joints;
Cruciate ligament reconstruction

Summary

Objectives: We investigated the effectiveness of homeopathic *Arnica montana* on postoperative swelling and pain after arthroscopy (ART), artificial knee joint implantation (AKJ), and cruciate ligament reconstruction (CLR).

Design: Three randomised, placebo-controlled, double-blind, sequential clinical trials.

Setting: Single primary care unit specialised in arthroscopic knee surgery.

Participants: Patients suffering from a knee disease that necessitated arthroscopic surgery.

Interventions: Prior to surgery, patients were given 1 × 5 globules of the homeopathic dilution 30× (a homeopathic dilution of 1:10³⁰) of arnica or placebo. Following surgery, 3 × 5 globules were administered daily.

Primary outcome measures: The primary outcome parameter was difference in knee circumference, defined as the ratio of circumference on day 1 (ART) or day 2 (CLR and AKJ) after surgery to baseline circumference.

Results: A total of 227 patients were enrolled in the ART (33% female, mean age 43.2 years;), 35 in the AKJ (71% female, 67.0 years), and 57 in the CLR trial (26% female; 33.4 years). The percentage of change in knee circumference was similar between the treatment groups for ART (group difference $\Delta = -0.25\%$, 95% CI: -0.85 to 0.41 , $p = 0.204$) and AKJ ($\Delta = -1.68\%$, -4.24 to 0.77 , $p = 0.184$) and showed homeopathic arnica to have a beneficial effect compared to placebo in CLR ($\Delta = -1.80\%$, -3.30 to -0.30 , $p = 0.019$).

[☆] This trials were funded by the Karl und Veronica Carstens Foundation, a member of the Stifterverband fuer die deutsche Wissenschaft. Trial medication was manufactured by DHU in Karlsruhe, Germany.

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Conclusions: In all three trials, patients receiving homeopathic arnica showed a trend towards less postoperative swelling compared to patients receiving placebo. However, a significant difference in favour of homeopathic arnica was only found in the CLR trial. © 2006 Published by Elsevier Ltd.

Introduction

Arthroscopy of the knee is one of the most common surgical interventions. The success of arthroscopy depends to some extent on effectively controlling and treating postoperative pain and swelling.^{1,2}

Analgesic approaches include systemic opiates or systemic non-steroidal anti-inflammatory drugs (NSAIDs). The intra-articular application of local anesthetics,³ NSAIDs,^{4,5} cortisone preparations,⁶ and intra-articular opioids^{7,8} has been proven effective. Various therapies such as cold treatment,^{9–11} Cryo/Cuff² and compression¹² have been shown to have positive effects on postoperative swelling, but are expensive, time-consuming and labour intensive. Additionally, both the systemic and local application of analgesics, anaesthetics, or cortisone may be accompanied by side effects including fatigue, bleeding, or local infections.

Arnica montana (fam. compositae), commonly known as leopard's bane, is widely used as a herbal remedy or homeopathic dilution to improve wound healing. To date, approximately 40 clinical trials on homeopathic arnica have been conducted. Eleven of these have dealt with the prevention of posttraumatic and postoperative wound healing disorders.¹³ A systematic review of placebo-controlled clinical trials suggests that homeopathic arnica is not effective for this indication.¹⁴ However, the review did not include all available trials,¹³ and most of the trials it did include had severe methodological shortcomings.¹⁴

The aim of the three randomised clinical trials described here was to investigate the effectiveness and safety of homeopathic arnica 30 \times (a homeopathic dilution of 1:10³⁰) on postoperative swelling and pain after arthroscopy (ART), artificial knee joint implantations (AKJ), and cruciate ligament reconstructions (CLR).

Methods

Design and patients

We conducted three single centre, randomised, placebo-controlled, double-blind sequential tri-

als,¹⁵ each with two parallel therapy groups, of which one received placebo and the other with arnica 30 \times .

Sequential trials are a rather new type of controlled clinical investigation. Data from a sequential clinical trial are accumulated successively: every time a patient's outcome data become available, the group differences are evaluated immediately. The trial is terminated when the path of the *t*-statistic, which measures imbalance between the outcome for the two randomised groups, crosses one of the preset termination boundaries ("efficacy", or "no difference in outcome"). Termination boundaries must reflect the nature of the entire test procedure, which evaluates the data repeatedly. When represented as a diagram, these boundaries form a triangle. The test procedure is referred to as a "triangular test". The main advantage of sequential trials is that they can be stopped early, providing that there is enough evidence for or against the active treatment.

All three of the trials discussed here were conducted at the Department of Accident Surgery at Kulmbach Hospital in Bavaria, Germany. Patients were treated and followed up for 2 (ART), 8 (CLR), or 11 days (ARJ).

The study was performed according to common guidelines for clinical trials. The protocol was approved by the ethics review board of the University of Erlangen-Nuremberg. All study participants provided written, informed consent and were insured according to the German law for medicinal products.

Patients were recruited consecutively from the Department of Accident Surgery at Kulmbach Hospital in Bavaria, Germany. Inclusion criteria were: patients of both genders, age 18–75 years, written consent, knee diseases necessitating arthroscopy, artificial knee joint implantations, or cruciate ligament reconstructions. Exclusion criteria were identical in all three trials and included recent traumas, acute knee inflammation, autoimmune disease, tumour diseases, alcohol abuse, serious systemic mental or physical disease, severe allergic disease, pregnancy, breast feeding, regular analgesic consumption, drug abuse, or participation in another clinical trial.

Randomisation, blinding, and monitoring

For each indication group, the responsible biometrician (RL) compiled a separate randomisation list. Patients were allocated to one of the two therapies using unstratified block randomisation with a block length of 10. The trial medication was sent by the manufacturer (DHU, Karlsruhe, Germany) to the biometrician in labelled vials which were then relabelled according to the randomisation list. Relabelling was done on blank stickers stating only the intended purpose, indication group, and running patient number.

The randomisation list was kept by the biometrician and the sponsor. The list was therefore not available to the investigator until the final biometrical report completed. Although unblinding was declared permissible in individual cases, no use was made of this. The trial was monitored by the biometrician and, additionally, by an independent expert who was not involved in any other aspect of the trial.

Study interventions

The *A. montana* used in the trials was manufactured as a homeopathic dilution (Arnica 30 \times) by the Deutsche Homoeopathische Union (DHU) in Karlsruhe, Germany in accordance with the Guidelines of the *German Homoeopathic Pharmacopoeia*. In arnica 30 \times , arnica is diluted 30 times with water, each dilution in the proportion 1:1. It was administered orally with sucrose globules as the carrier substance. Placebo consisted of sucrose globules alone and did not differ from the arnica treatment in size, colour, or taste.

Administration of the study medication began with five globules approximately 2 h before surgery. Postoperatively, on the day of the surgery, patients were given 3 \times 5 globules at 3 h intervals after the recovery phase. Starting on the second postoperative day, five globules three times a day until the last scheduled follow-up examination.

The trial medication was administered as a supplement to routine treatment. Both the operation procedure itself and postoperative care were conducted according to the usual standards throughout the study. All surgical procedures on cruciate ligaments were performed either by the chief physician of the hospital or by experienced senior physicians. Surgery was performed after prior arthroscopy using the middle third of the patellar tendon for a ligament prosthesis and under continued arthroscopic control. All patients received heparin for thrombosis prophylaxis. Additional pain therapy was available on request.

Outcome measures

Outcome parameters were measured preoperatively and then daily until postoperative day 2 in ART patients, additionally on days 3, 5, and 8 in the other two trials, and once more on day 11 in AKJ patients. The primary outcome parameter was the relative change in knee circumference, defined as the ratio of circumference on day 1 (ART) or day 2 (CLR and AKJ) after surgery to baseline circumference. Knee circumference was measured with a measuring tape placed around the middle of the patella and the popliteal space. Measurements were performed by a single investigator (JW) and made to the millimetre three times in succession and then averaged.

Secondary outcome parameters included pain and the number of unexpected events. Pain intensity was determined in the morning using a 100 mm VAS. The quantity of analgesics taken, frequency of drainage, quantity of drainage fluid collected, and quantity of postoperative puncture fluid were recorded.

Statistics

The statistical evaluation for each trial was conducted separately. Effectiveness analyses were based on an intention-to-treat (ITT) population. All patients who had taken the trial medication and undergone the planned operation were included in the ITT analysis. Safety was assessed on the basis of all participating patients, including those who did not undergo the operation. Missing values were replaced, if necessary, by the last-observation-carried-forward method. Results are always given in frequency counts or as the mean (standard deviation). The main analysis in our trials relied on two-sided triangle tests, which assessed the effectiveness of arnica separately for each type of surgery. These were also used to calculate Cohen's *d* effect sizes and 95% confidence intervals (CI).¹⁵ In addition, we pooled the data from all three trials as part of a post hoc analysis and constructed an ANCOVA model regressing the percentage change to the baseline knee circumference (linear regressor), the type of surgery (ART, CLR, or ARJ), the treatment (verum or placebo), and the surgery–treatment interaction.

In a sequential trial, the number of patients cannot be calculated a priori: because the trial is stopped as early as possible, the actual number of patients differs from trial to trial. Nevertheless, it is possible to calculate the number of patients one expects in an average trial;

this number depends on the mean effect size and the predefined power of the statistical test procedure. In all three trials, the distribution of each outcome parameter was taken to be Gaussian, but different effect sizes were assumed for each trial. The expected number of patient was calculated to be 230 for ART, 61 for CLR, and 24 for AKJ. These calculations were based on the assumption that the knee would be swollen by 2.4% in ART (CLR: 4.8%, AKJ: 6.5%) patients treated with placebo, and by 1.9% (3.7%, 4.4%) in verum patients. The standard deviations were taken as 1.5% in ART, 1.7% in CLR, and 2.0% in AKJ. For each trial, we allowed for a type I error of $\alpha = 5\%$ and a power in verifying the above figures of $\beta = 90\%$ (calculated with the PEST[®] software package).¹⁶

Results

From November 1996 to December 1997, a total of 343 patients were included in the three trials: 237 in ART, 35 in AKJ, and 71 in CLR (Fig. 1a–c). In total, 21 patients did not receive the surgery that had originally been planned. A total of 12 patients who originally planned to undergo only CLR were examined by ART. Conversely, five scheduled ART patients underwent CLR. In four patients, the surgery was cancelled for organisational reasons unrelated to the therapy under study. Three patients in the ART trial were lost to follow-up before surgery, but after randomisation, because of anxiety about the procedure. All of these seven patients were excluded from evaluation in accordance with the trial protocol, which meant that data were available for 227

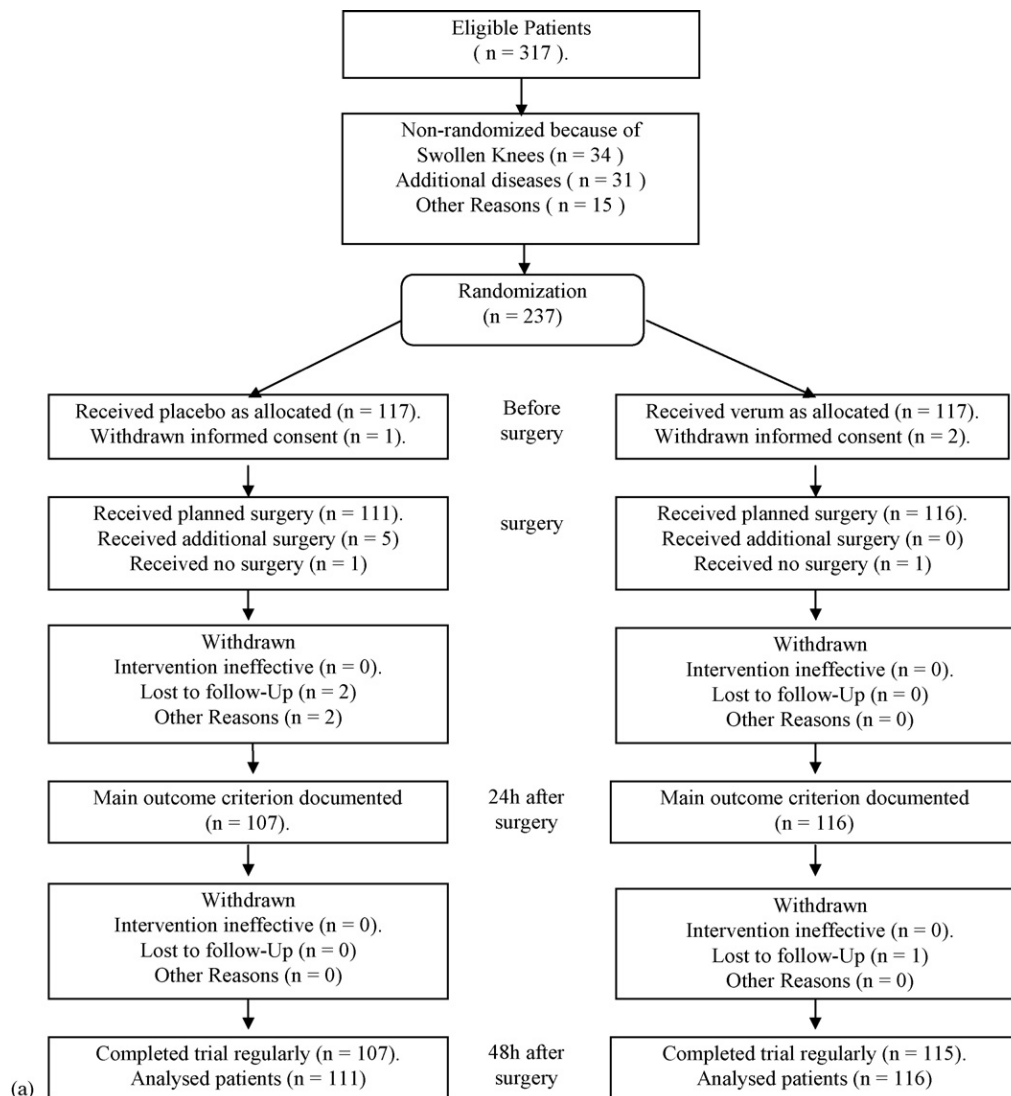


Figure 1a Flow-diagram of ART trial.

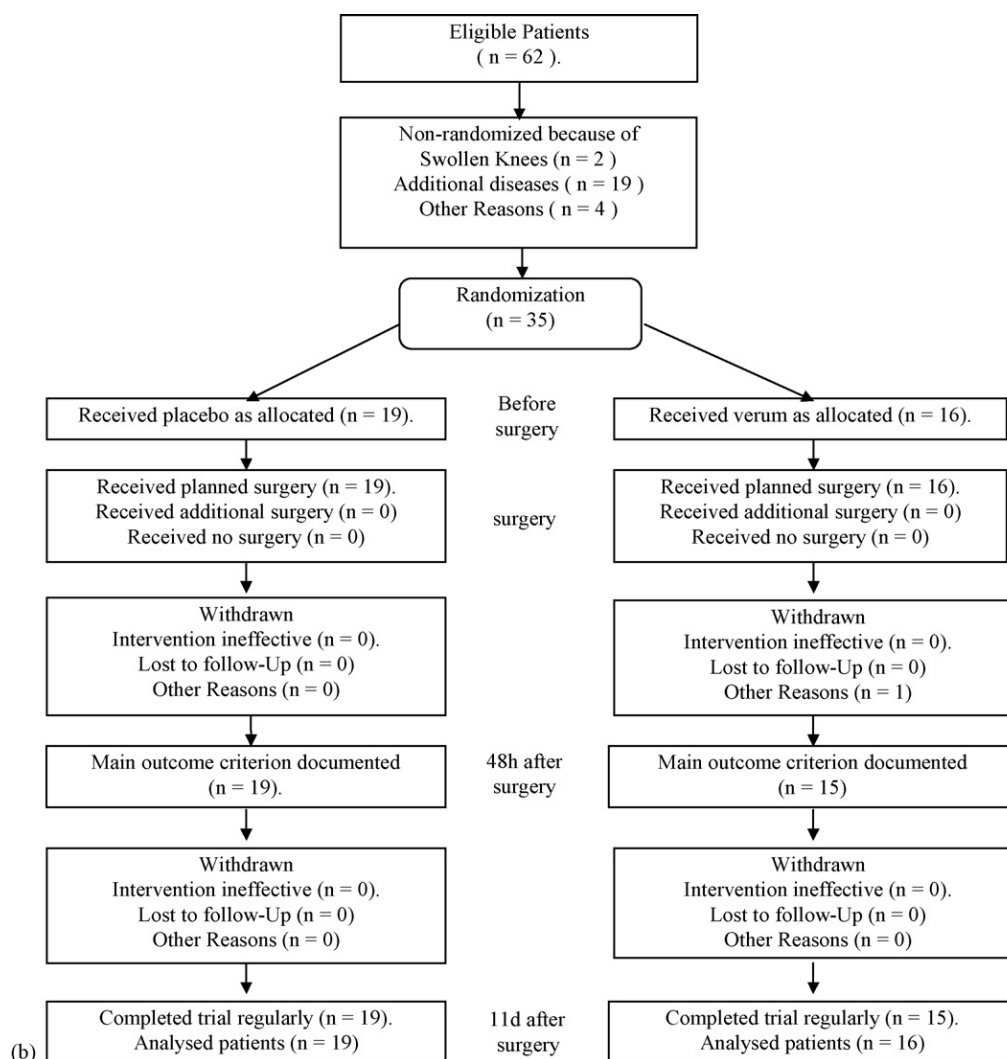


Figure 1b Flow-diagram of AKJ trial.

ART patients (arnica: 111, placebo: 116), 35 AKJ patients (16 versus 19), and 57 CLR patients (30 versus 27). The decision about whether to exclude a patient from evaluation was made before the code had been disclosed and without knowing the primary outcome.

In each of the three trials, therapy groups were comparable in terms of demography and medical history (Table 1). In particular, there were no substantial differences in baseline knee circumference values. The only remarkable differences relate to the type of anaesthesia used. In the ART trial, 40% of placebo patients, but only 21.5% of verum patients, were given general anaesthesia, whereas in the CLR the relationship (15% of placebo patients versus 37% of verum patients) was more or less reversed.

One ART patient in the arnica group lost his medication, which, according to the examining physi-

cian, he had never taken. He was re-randomised, this time to the placebo group. The case record forms of two other ART patients (one placebo, one arnica) were lost, but the values for the main outcome criterion were still available. The emergency code was not opened for any of the patients.

There was one drop-out during the course of the trial, as one ART patient withdrew his consent after randomisation. Compliance to medication was generally good. One ART patient (arnica) forgot to take his globules preoperatively, and one placebo patient with AKJ was given wrongly arnica 30 \times .

For all three knee surgery procedures, knee swelling in patients who received arnica 30 \times was less severe on the first 2 postoperative days than in the placebo group (Table 2). The treatment differences were significantly different for CLR ($p=0.019$), but not for AKJ ($p=0.184$) or ART

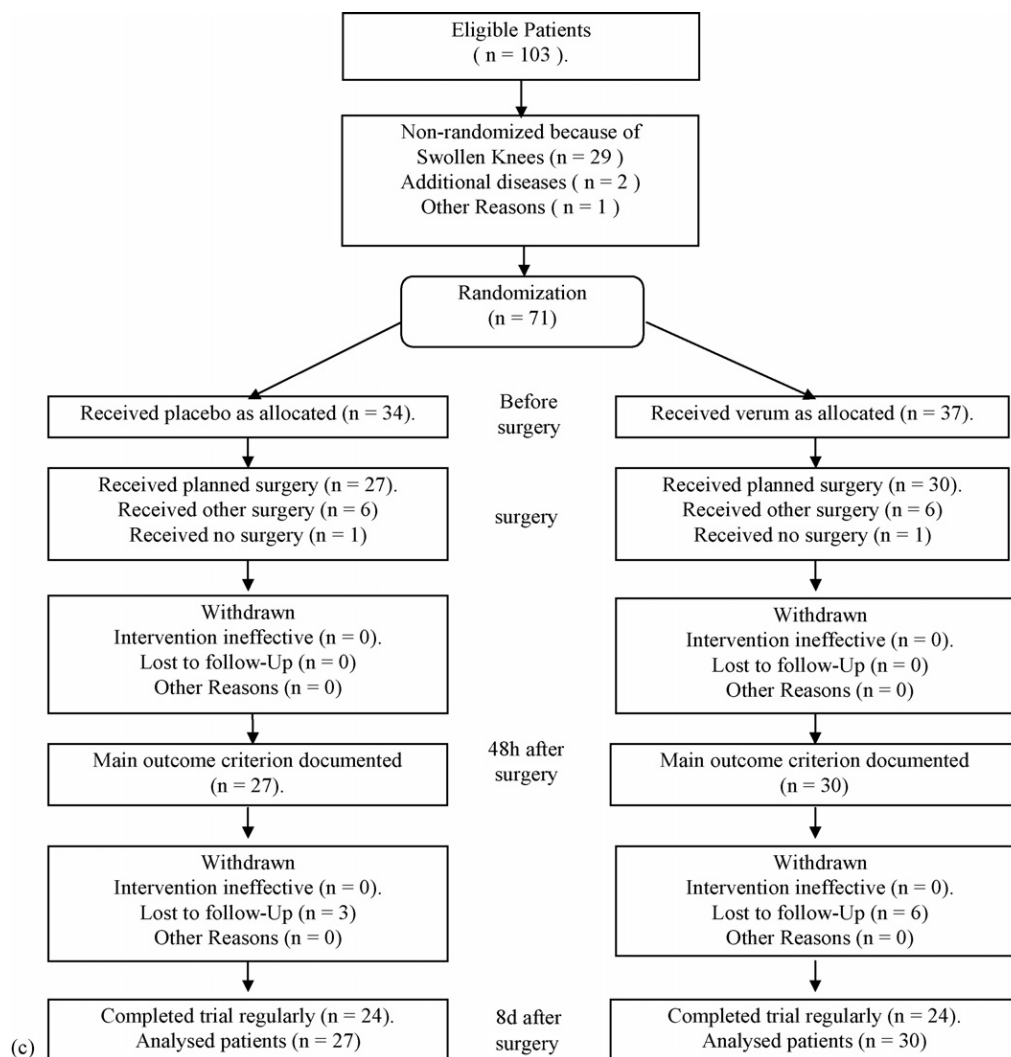


Figure 1c Flow-diagram of CLR trial.

($p = 0.204$) (Table 3). Combining the three p -values according to Fisher's inverse chi-square-method¹⁷ also confirmed the hypothesis that at least one trial would show a treatment effect ($p = 0.005$, one-sided).

Pooling the individual patient data from all three trials in a post hoc analysis, demonstrated an overall treatment effect ($p = 0.040$, ANCOVA F -test), but did not show any interaction between treatment effect and type of surgery ($p = 0.333$, ANCOVA F -test). Thus, there is no strong evidence that the effectiveness of arnica depends on which surgery was performed.

The reduction in swelling after CLR could be observed on day 1 as well as on day 2 and, to a smaller degree, on all subsequent days (Fig. 2). In contrast, after AKJ, the effect was neither constant over time, nor significant at any point. Clinically and statistically, the effect after ART was small, both on days 1 and 2.

The effect pattern for pain was similar to that seen for swelling (Fig. 3). In general, there was a tendency in favour of verum for all three indications. In the CLR trial, effect sizes were much smaller and not statistically significant at any point in time, not even on day 1. With AKJ, there were two points in time (days 2 and 11) at which verum seemed to be slightly inferior to placebo, but again this effect cannot be confirmed statistically.

None of the results were affected by the use of analgesics: all treatment effects and p -values remained nearly unchanged when the anti-inflammatory or analgesic effects of additional medications are incorporated into the statistical analysis. The total amount of analgesics used on day 1 was similar in the verum and the placebo groups. This pattern also applies to other analgesics and the following days. Surprisingly, additional statistical analyses showed no correlation between pain and previous use of analgesics.

Table 1 Baseline characteristics

	ART		AKJ		CLR	
	Arnica	Placebo	Arnica	Placebo	Arnica	Placebo
Women/men	36/75	39/76	13/3	12/7	7/23	8/19
Age [years]	42.2 (14.5)	44.1 (14.8)	67.9 (5.2)	66.2 (4.9)	35.2 (10.7)	31.4 (7.3)
Median, range	38 (32–56)	43 (33–58)	69 (64–72)	66 (62–69)	30 (27–42)	37 (27–36)
Previous knee surgery (yes/no)	35/76	27/89	3/13	8/11	17/13	13/14
Accompanying illness (yes/no)	8/103	13/102	1/15	8/11	0/30	0/27
Duration of complaints ^a [months and years]; median, range	31 (63); 8 (2–24)	34 (79) 6; (2–24)	8 (7); 6 (3–10)	10 (9); 8 (3–10)	55 (109); 2 (1–24)	35 (89); 4 (0–17)
Preoperative knee circumference [mm]	396 (27)	399 (30)	423 (34)	426 (36)	393 (22)	388 (22)
Perioperative complications (yes/no)	0/111	3/113	1/15	0/19	0/30	2/25
Duration of surgery [min]	66 (18)	62 (17)	112 (14)	117 (15)	123 (17)	121 (18)

Abbreviations: ART, arthroscopies; CLR, cruciate ligament reconstruction; AKJ, artificial knee joint implantation. Results are given in frequencies or mean (standard deviation).
^a Duration of complaints is measured in months (ART and CLR) or years (AKJ).

Table 2 Results for the primary and secondary outcome parameters in the three trials

	ART		AKJ		CLR	
	Arnica, <i>m</i> (S.D.)	Placebo, <i>m</i> (S.D.)	Arnica, <i>m</i> (S.D.)	Placebo, <i>m</i> (S.D.)	Arnica, <i>m</i> (S.D.)	Placebo, <i>m</i> (S.D.)
Knee circumferences day 1 [mm]	397 (26)	401 (31)	431 (24)	434 (41)	396 (19)	399 (24)
Knee circumferences day 2 [mm]	400 (26)	403 (32)	435 (28)	444 (38)	402 (19)	407 (25)
Primary outcome						
Change of knee circumferences, day 1 [%]	0.07 (2.21)	0.32 (2.38)	−0.25 (−0.85; 0.41)	0.20	0.89 (2.77)	2.68 (2.98)
Change of knee circumferences, day 2 [%]	0.88 (2.44)	1.05 (2.57)	−0.17 (−0.83; 0.49)	0.61	3.43 (2.68)	4.75 (2.78)
Secondary outcomes						
Change of knee circumferences, day 1 [mm]	0.1 (8.8)	1.2 (9.6)	−1.2 (−3.6; 1.1)	0.30	3.2 (10.5)	10.3 (11.7)
Change of knee circumferences, day 2 [mm]	3.3 (9.6)	4.1 (10.3)	−1.0 (−3.6; 1.6)	0.45	13.2 (9.9)	18.4 (10.7)
Pain, day 1 [mm]	23 (16)	24 (18)	−1.5 (−6.1; 3.2)	0.53	27 (18)	37 (17)
Pain, day 2 [mm]	13 (18)	14 (20)	−1.4 (−6.4; 3.6)	0.58	20 (17)	23 (19)
Number of punctures	0.3 (0.6)	0.3 (0.6)	0.0 (−0.2; 0.2)	0.97	1.1 (1.2)	1.3 (1.5)
Amount of puncture fluid [ml]	8 (27)	8 (33)	0.6 (−7.4; 8.5)	0.89	38 (57)	50 (59)
Total drainage fluid [ml]	198 (128)	194 (140)	4 (−32; 40)	0.82	342 (260)	327 (263)

Abbreviations: ART: arthroscopies; CLR: cruciate ligament reconstruction; AKJ: artificial knee joint implantation; *m*: mean; S.D.: standard deviation; Δ : mean difference between groups.

Table 3 Therapeutic effects with respect to swelling (change of knee circumference)

	ART	AKJ	CLR
Standard effect	0.11	0.48	0.66
95% CI	-0.18 to 0.37	-0.22 to 1.21	0.11–1.21
<i>p</i> -Value (two-sided)	0.204	0.184	0.019

For Abbreviations, see Table 1. Standardised effects are defined as the ratio of the difference of means and the pooled pretreatment standard deviation. Positive values indicate superiority of Arnica.

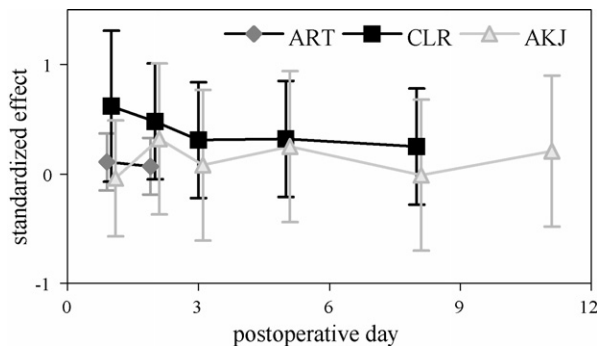


Figure 2 Effects on swelling over time (standardised effects and 95% confidence intervals) (legend see Table 3).

We were unable to find differences between arnica 30 \times and placebo in any of the three trials with regard to the total amount of drainage fluid ($p > 0.5$ in each trial), number of punctures ($p > 0.5$ in each trial), or the total amount of liquid removed by puncture ($p > 0.3$ in each trial) (Table 2).

No relevant differences, either in laboratory parameters or in blood conserves, were found in the ART or CLR trials. Obvious differences in treatment groups occurred in the AKJ trial. The mean pre-to-postoperative difference was -31.5 (30.3) $\times 1000$ platelet cells/l in the placebo group, compared to -83.5 (36.9) in the verum group on the first postoperative day.

The number of patients who experienced Adverse events (AEs) was low. Although there was a tendency towards a reduced number of AEs in the

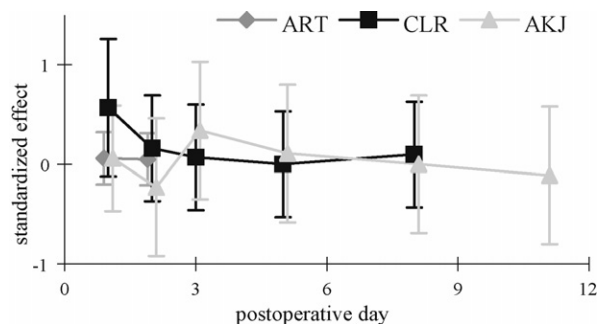


Figure 3 Effects on pain over time (standardised effects and 95% confidence intervals) (legend see Table 3).

arnica groups, the observed differences of 5 versus 8 (ART), 3 versus 7 (AKJ), and 3 versus 4 (CLR) were not statistically significant. None of the events were classified as being related to the study medication. The trend in favour of arnica 30 \times remains observable even if serious adverse events (SAEs) are considered. Within the first 3 months after surgery we documented 2 versus 6 (ART), and 1 versus 4 (AKJ) SAEs.

Discussion

Our findings show that homeopathic arnica was more effective in reducing postoperative swelling than placebo in CLR, whereas there were no significant differences between either intervention in ART and AKJ.

This trials are some of the largest and most rigorous investigations to examine the efficacy of homeopathic arnica on postoperative pain or swelling to date. Its strengths include an innovative study design and rigorous methodology.

For practical reasons, and due to the nature of the side-effects caused by arthroscopy, the period over which study patients were observed and during which follow-up data were collected was 48 h in the arthroscopy trial. We did not record any long-term follow-up data. This was done in good accordance with most other trials that have investigated the treatment of postoperative arthroscopy swelling and pain to date, as these have also measured the outcome parameter within the 48 h following the operation.^{1,2,4} In contrast to our study, patients in several other studies were contacted at weeks 1 and 2 following study completion and asked to fill out a written follow-up questionnaire.¹²

The sequential design of the trials helped us to minimise the number of patients, time, and money needed to conduct the trial. For example, if we had used a fixed sample size design in the ART trial, we would have needed 382 patients rather than the 227 enrolled in our trial—a 40.4% reduction. This was possible because of the nature of sequential trials, which focus exclusively on a single outcome parameter and a single statistical test. Consequently, analysing the data with methods other

than those which were prespecified – for example, using a different target measure – would lead to suboptimal or even invalid results. In sequential trials, switching the analysis means a loss of statistical power. A suggestion was made to reanalyse our trial, using the absolute change in knee circumference (rather than the percentage change) as the main outcome parameter and applying ANCOVA models (rather than the triangular test) to our data. However, it is not surprising that if we were to follow this suggestion, the *p*-values would increase (ART: *p* = 0.30; CLR: *p* = 0.08; AKJ: *p* = 0.25) compared to those seen in our original analyses.

Additional analyses show that our data meets the statistical assumptions for a triangle test and that the results obtained here are robust with respect to deviations from the selected statistical analysis, as they are with respect to the choice of the study population. The latter can be seen in the fact that the results of the CLR trial remain statistically significant (*p* = 0.034) even when those patients are included who were randomised for CLR but only underwent ART. Using ANOVA models, we were unable to confirm any effects based on the type of anaesthesia used in the ART (*p* = 0.251) or CLR trials (*p* = 0.713). *p*-Values for treatment effects remained nearly constant. We therefore assume that the reported anaesthesia imbalances did not affect the results substantially.

In previously published trials, complication rates have ranged from 0.01 to 0.78%.^{18–20} In contrast to this, our study showed a complication rate following ART of almost 2%. This discrepancy may be due to the fact that the abovementioned studies were based on retrospective surveys and therefore may have tended to underestimate complication rates. A prospective study by Small²¹ on more than 10000 patients undergoing ART showed a complication rate of 1.68%, whereas Sherman et al. found a remarkable 8.2%.²²

Studies investigating the effectiveness of cryotherapy, Cryo/Cuff, and pain wrap also found less swelling in patients who underwent knee arthroscopy.^{2,12} These trials had methodological restrictions, which were primarily due to the size of the study population and the lack of patient blinding to the study interventions. However, in both trials mentioned above, the clinical effects were small, and there were no significant improvements in swelling compared to the control treatments. To date, none of the available literature has provided data on the point at which a reduction in postoperative swelling becomes clinically relevant. However, cryotherapy, Cryo/Cuff, and pain wrap are time-consuming and labour intensive and have yielded results comparable to those seen with

arnica with regard to postoperative swelling. In this context, arnica seems a low-cost alternative to treat postoperative swelling.

Previous studies examining the influence of NSAIDs almost exclusively deal with pain as the primary outcome parameter.^{4–6,23} The results obtained in these trials indicate that NSAIDs are more effective than arnica as painkillers. However, the fact that arnica in our trial was only used as a supplement to NSAIDs rather than as an exclusive treatment makes the studies difficult to compare.

In total, we were able to find almost 40 studies of arnica applied in homeopathic dosages or as part of complex homeopathic preparations.¹³ The great majority of these were randomised, double-blind studies. A total of 13 showed a significantly positive result in favour of verum, whereas 10 show at least a tendency in favour of verum. Only one study showed a clearly negative outcome. In their entirety, homeopathic studies on arnica therefore appear to confirm the overall assessment of homeopathy presented by Linde et al.²⁴ This finding is contested by a meta-analysis of eight studies which came to the conclusion that “the trial data do not support the notion that arnica is efficacious”.¹⁴ The reason for this discrepancy may lie in the specific indication of arnica for soft tissue traumas, which was also the subject of the present study. If this indication is taken alone, the ratio of positive to negative studies shows a shift in favour of a homeopathic effect (6 out of 14 significantly positive, 5/14 with a positive tendency, 3/14 without any tendency).¹³

Conclusions

In all three trials, patients receiving homeopathic arnica showed a trend towards less postoperative swelling compared to patients receiving placebo. However, a significant difference was found only in the CLR group, but not for ART or AKJ. Because arnica is a low-cost alternative compared to other treatments that have shown comparable results, even minor reductions in swelling and pain seem to justify the use of homeopathic arnica in CLR.

Acknowledgements

We would like to thank R. Alpermann, Institute for Medical Information Processing, University of Tübingen, for her assistance in monitoring the trial. We also express our gratitude to all patients who participated in the study.

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