Methylprednisolone Injections for the Carpal Tunnel Syndrome

A Randomized, Placebo-Controlled Trial

Isam Atroshi, MD, PhD; Magnus Flondell, MD; Manfred Hofer, BSc; and Jonas Ranstam, PhD

Background: Steroid injections are used in idiopathic carpal tunnel syndrome (CTS), but evidence of efficacy beyond 1 month is lacking.

Objective: To assess the efficacy of local methylprednisolone injections in CTS.

Design: Randomized, placebo-controlled trial. (ClinicalTrials.gov: NCT00806871)

Setting: Regional referral orthopedic department in Sweden.

Patients: Patients aged 18 to 70 years with CTS but no previous steroid injections.

Intervention: Three groups (37 patients each) received 80 mg of methylprednisolone, 40 mg of methylprednisolone, or placebo. The patients and treating surgeons were blinded.

Measurements: Primary end points were the change in CTS symptom severity scores at 10 weeks (range, 1 to 5) and rate of surgery at 1 year. Three patients had missing 10-week data. All patients had 1-year data.

Results: Improvement in CTS symptom severity scores at 10 weeks was greater in patients who received 80 mg of methylprednisolone than in those who received placebo (difference in change from baseline, −0.64 [95% CI, −1.06 to −0.21; P = 0.003] and −0.88 [CI, −1.30 to −0.46; P < 0.001], respectively), but there were no significant differences at 1 year. The 1-year rates of surgery were 73%, 81%, and 92% in the 80-mg methylprednisolone, 40-mg methylprednisolone, and placebo groups, respectively. Compared with patients who received placebo, those who received 80 mg of methylprednisolone were less likely to have surgery (odds ratio, 0.24 [CI, 0.06 to 0.95]; P = 0.042). With time to surgery incorporated, both the 80- and 40-mg methylprednisolone groups had lower likelihood of surgery (hazard ratio, 0.46 [CI, 0.27 to 0.77; P = 0.003] and 0.57 [CI, 0.35 to 0.94; P = 0.026], respectively).

Limitation: The study was conducted at 1 center, and wrist splinting had previously failed for all patients.

Conclusion: Methylprednisolone injections for CTS have significant benefits in relieving symptoms at 10 weeks and reducing the rate of surgery 1 year after treatment, but 3 out of 4 patients had surgery within 1 year.

Primary Funding Source: Region of Scania Research and Development Foundation and Hässleholm Hospital Organization.

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Methods

Design Overview

The study was a prospective, randomized, placebo-controlled, parallel-group trial that compared local injections of 80 mg of methylprednisolone, 40 mg of methylprednisolone, and placebo (1:1:1 ratio) in patients with idiopathic CTS who were not previously treated with steroid injections. The patients and orthopedic surgeons who administered the interventions were blinded. The trial has been previously described (10). Enrollment started in November 2008, and follow-up was completed in March 2012. The trial was approved by the Swedish Medical Products Agency, Uppsala, Sweden, and the Ethics Committee at Lund University, Lund, Sweden.

Setting and Participants

Patients referred by primary care physicians to 1 orthopedic department for evaluation were examined by trial investigators (orthopedic surgeons) and screened for eligibility. The inclusion criteria were primary idiopathic CTS.

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Context

The carpal tunnel syndrome (CTS) is very common. Steroid injections are often used to alleviate CTS symptoms and prevent the need for surgery.

Contribution

In a trial of patients with mild to moderate CTS who were unsuccessfully treated with wrist splinting, those who received methylprednisolone were somewhat less likely to have had surgery at the 1-year follow-up than those who received placebo. Nonetheless, 3 out of 4 patients who received methylprednisolone had surgery within 1 year.

Caution

Patients with severe CTS were excluded. Wrist splinting had failed for all patients before enrollment.

Implication

In most patients with CTS, methylprednisolone temporarily improves symptoms but does not obviate the need for surgery.

—The Editors

age 18 to 70 years, symptoms of classic or probable CTS (numbness or tingling in at least 2 of the 4 radial fingers) according to the Katz diagnostic criteria (11, 12), unsuccessful 2-month treatment with wrist splinting, symptom severity that warranted referral for consideration for surgery, and nerve conduction test results that showed median neuropathy at the wrist. If nerve conduction test results were normal, 2 orthopedic surgeons independently diagnosed the patient with CTS. The exclusion criteria were previous steroid injection, thenar muscle atrophy, sensory loss (2-point discrimination >8 mm), diabetes mellitus, thyroid disorder, inflammatory disease, polyneuropathy, current pregnancy, previous carpal tunnel release, surgery on the contralateral hand in the past 2 months, inability to respond to questionnaires, severe illness, and drug or alcohol abuse.

Randomization and Interventions

A statistician made a computer-generated randomization list (3 groups; 1:1:1 ratio) in varying blocks. Sequentially numbered, opaque, concealed envelopes containing group assignments were prepared. A trial investigator (orthopedic surgeon) asked eligible patients whether they would participate in this trial. Participants could choose to have surgery 3 months after enrollment if they did not improve. After providing written informed consent, the patients were randomly assigned to 1 of 3 trial groups: 2 mL (80 mg) of methylprednisolone plus 1 mL of lidocaine, 1 mL (40 mg) of methylprednisolone plus 1 mL of saline plus 1 mL of lidocaine, or 2 mL of saline plus 1 mL of lidocaine. Randomization was done by the study nurse, who opened the envelope containing the group assign-

ment. In bilateral symptoms, the most symptomatic hand (identified by the patient as the main source of symptoms and activity limitations) was treated. Most patients had no symptoms or less pronounced symptoms in the nonstudy hand. The nurse prepared the injection in a covered syringe to mask the orthopedic surgeon and patient immediately after randomization. The injection was then administered subfascially in the soft tissues of the carpal tunnel by the surgeon using standard technique. The needle was inserted 1 cm proximal to the wrist crease, ulnar to the midline, and advanced in a 45- to 60-degree angle to the forearm (10, 13). While the needle was withdrawn, a dressing was pressed over the puncture site to conceal the color (placebo was clear, and methylprednisolone was cloudy) in case of leakage. The patients were instructed to use their hands as tolerated; no other treatments were given.

Outcomes and Follow-up

The primary end points were the change in CTS symptom severity score at 10 weeks and the rate of surgery at 1 year. The secondary end points were time to surgery; change in CTS symptom severity score at 1 year; the short Disabilities of the Arm, Shoulder and Hand (QuickDASH) score; Short Form-36 (SF-36) Health Survey bodily pain score; SF-6D score; and treatment satisfaction at 10 weeks and 1 year.

Baseline assessment included demographics, medical history, and Phalen and Tinel tests. The patients completed the 11-item CTS symptom severity scale, the 11-item QuickDASH, and SF-6D survey. The symptom severity scale measures severity, frequency, and duration of nighttime and daytime pain and numbness or tingling (14) with a score from 1 (no symptoms) to 5 (most severe). QuickDASH measures difficulties in performing daily activities (15) with a score from 0 (no disability) to 100 (worst). The SF-6D survey, which consists of 11 SF-36 items, including the 2 on bodily pain, yields an index from 0.3 (worst health) to 1 and a bodily pain score from 0 (worst) to 100 (16, 17).

Physical examinations done by the physical therapist for the study included measurement of hand strength (grip and pinch) and sensation (monofilament and 2-point discrimination). Nerve conduction testing was done by measuring median nerve sensory latency from the wrist to the index finger and difference between median and ulnar sensory latency from the wrist to the ring finger. The results were classified by a neurophysiologist; difference in sensory latency less than 0.6 ms was considered normal, 0.6 to 0.9 ms was mild, 1.0 to 1.6 ms was moderate, and 1.7 ms or greater or absent response was considered severe (18). The test results were not used to influence patients’ decisions about treatment or selecting a study hand in bilateral symptoms. Patients were not aware of the actual test results to avoid possible influence on patient-reported outcomes.

At 5 weeks after injection, a telephone interview was done by a blinded trial orthopedic surgeon. During the interview, the surgeon asked if the patient noted a difference in the affected hand. The nurse prepared the injection in a covered syringe to mask the orthopedic surgeon and patient immediately after randomization. The injection was then administered subfascially in the soft tissues of the carpal tunnel by the surgeon using standard technique. The needle was inserted 1 cm proximal to the wrist crease, ulnar to the midline, and advanced in a 45- to 60-degree angle to the forearm (10, 13). While the needle was withdrawn, a dressing was pressed over the puncture site to conceal the color (placebo was clear, and methylprednisolone was cloudy) in case of leakage. The patients were instructed to use their hands as tolerated; no other treatments were given.

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At 5 weeks after injection, a telephone interview was done by a blinded trial orthopedic surgeon. During the interview, the surgeon asked if the patient noted a difference in the affected hand.
interview, the patients gave their responses to the items in the CTS symptom severity scale, QuickDASH, and SF-6D survey and rated treatment satisfaction on a visual analog scale from 0 (very dissatisfied) to 100 (completely satisfied). During follow-ups visits at 10, 24, and 52 weeks, the patients completed the CTS symptom severity scale, QuickDASH, and SF-6D survey; rated treatment satisfaction; and had physical examinations. Before examination by the physical therapist, the nurse covered the patient’s palm with a dressing to conceal a possible surgical scar.

Patients who pursued surgery on the study hand were operated on with open carpal tunnel release by surgeons not involved in the trial. The decision to pursue surgery was made solely by the patient without influence from the investigators, in accordance with the trial protocol.

At each follow-up, the trial orthopedic surgeon asked about specific adverse events (AEs), including pain, swelling, and numbness and allowed the patients to report any symptoms after the injection. All AEs were recorded on a standard AE form. Severity was rated (mild if there were no effects on daily activities, moderate if they caused difficulties in performing activities, and severe if they caused inability to perform activities). The onset and resolution dates of the AEs were recorded. Serious AEs included death, life-threatening diseases, diseases or symptoms warranting hospitalization or causing permanent disability, other important medical events, nerve injuries not normalized within 10 weeks, and infections requiring surgery.

During the trial, patients who required treatment of symptoms in the nonstudy hand were offered wrist splinting and surgery if splinting was ineffective. No patients were treated with injections.

Trial conduction and data collection were observed by a trial monitor. The patients and trial investigators (surgeons and physical therapists) remained blinded until all patients completed follow-up. After trial conclusion, the randomization codes were broken and the patients were informed of their group assignment.

Statistical Analysis

According to the pretrial sample size estimation (90% power and 5% significance level), the trial could detect a difference of 0.8 or greater in the symptom severity score (assumed SD of 1.0) between an intervention group and the placebo group when 102 patients were randomly assigned. In the protocol, we aimed to enroll 120 patients to compensate for withdrawals, but when the number of patients with complete follow-up exceeded the estimated sample size, we ended the trial after consulting with the statistician.

We analyzed the symptom severity score at 10 weeks using mixed-model analysis of repeated measures, adjusting for the baseline score. The results are presented as differences in mean score change over time and 95% CIs. For analysis of rate of surgery at 1 year, we used logistic regression; the odds ratios of having surgery within 1 year after injection were calculated. Adjustment for baseline variables (age, sex, duration of symptoms, dominance of treated hand, and symptom severity score) did not change the results of the logistic regression. As an alternative to odds ratios, we also calculated the relative risk for surgery within 1 year using a Cox regression analysis with constant time and robust variance estimates. We performed a Cox regression and calculated the hazard ratios of having surgery within 1 year after injection to incorporate time to surgery.

The proportional hazards assumption was investigated using scaled Schoenfeld residuals. All hypothesis tests of the assumption yielded statistically insignificant P values. Time to surgery was also analyzed with Kaplan–Meier curves, and the groups were compared with the log-rank test. The other secondary end points were analyzed with mixed models, adjusting for the baseline values. We did 3 prespecified subgroup analyses (symptom duration, median nerve conduction abnormality, and baseline symptom severity) for the change in symptom severity score at 10 weeks using mixed models with interaction terms (treatment by subgroup). For strength and sensation measures, we used mixed models to calculate the differences between groups in change over time, adjusting for the baseline values. Unless otherwise specified, the models (logistic regression, mixed models, and Cox regression) included only the treatment group and baseline value (when appropriate) as independent variables. Adverse events were tabulated, and groups were compared with the chi-square test when appropriate. All tests were 2-sided with a P value less than 0.05, indicating statistical significance. The analyses were done with higher priority for the 80-mg methylprednisolone versus placebo group followed by the 40-mg methylprednisolone versus placebo group and the 80-mg versus 40-mg methylprednisolone group (implying that less emphasis would be put on significant results in comparisons with lower priority unless the comparisons with higher priority were also significant). All participants were included in the analyses according to their randomization group assignment; the few missing data were not replaced. The analyses were done using Stata, version 12.1 (StataCorp, College Station, Texas), with logit for logistic regression, xtreg for mixed models, and stcox for Cox regression.

Role of the Funding Source

The study was supported by the Region of Scania Research and Development Foundation and Hössleholm Hospital Organization. The funding source had no role in the study design, conduct, and analysis; manuscript preparation or interpretation; or the decision to submit the manuscript for publication.

RESULTS

A total of 111 patients were randomly assigned. Thirty-seven patients received 80 mg of methylprednisolone injection; the odds ratios of having surgery within 1 year after injection were calculated. Adjustment for baseline variables (age, sex, duration of symptoms, dominance of treated hand, and symptom severity score) did not change the results of the logistic regression. As an alternative to odds ratios, we also calculated the relative risk for surgery within 1 year using a Cox regression analysis with constant time and robust variance estimates. We performed a Cox regression and calculated the hazard ratios of having surgery within 1 year after injection to incorporate time to surgery. The proportional hazards assumption was investigated using scaled Schoenfeld residuals. All hypothesis tests of the assumption yielded statistically insignificant P values. Time to surgery was also analyzed with Kaplan–Meier curves, and the groups were compared with the log-rank test. The other secondary end points were analyzed with mixed models, adjusting for the baseline values. We did 3 prespecified subgroup analyses (symptom duration, median nerve conduction abnormality, and baseline symptom severity) for the change in symptom severity score at 10 weeks using mixed models with interaction terms (treatment by subgroup). For strength and sensation measures, we used mixed models to calculate the differences between groups in change over time, adjusting for the baseline values. Unless otherwise specified, the models (logistic regression, mixed models, and Cox regression) included only the treatment group and baseline value (when appropriate) as independent variables. Adverse events were tabulated, and groups were compared with the chi-square test when appropriate. All tests were 2-sided with a P value less than 0.05, indicating statistical significance. The analyses were done with higher priority for the 80-mg methylprednisolone versus placebo group followed by the 40-mg methylprednisolone versus placebo group and the 80-mg versus 40-mg methylprednisolone group (implying that less emphasis would be put on significant results in comparisons with lower priority unless the comparisons with higher priority were also significant). All participants were included in the analyses according to their randomization group assignment; the few missing data were not replaced. The analyses were done using Stata, version 12.1 (StataCorp, College Station, Texas), with logit for logistic regression, xtreg for mixed models, and stcox for Cox regression.

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nisolone, 37 received 40 mg of methylprednisolone, and 37 received placebo (Figure 1). The baseline characteristics were generally similar among all groups (Table 1). All patients had complete baseline data. Two patients (1 each in the 80-mg methylprednisolone and placebo groups) chose to have surgery before the 10-week follow-up because of unchanged symptoms; these patients and another patient (placebo group) did not attend the 10-week examination and thus had no 10-week symptom severity score. All other patients had symptom severity scores, and any surgery occurred after the 10-week follow-up. Data about the 1-year rate of surgery were complete, and all patients were included in that analysis. No patient received injections in the study hand after the trial intervention. Twelve participants had surgery on the nonstudy hand during the 1-year study period (5, 4, and 3 patients in the 80-mg methylprednisolone, 40-mg methylprednisolone, and placebo groups, respectively). Eleven of these patients had surgery after they pursued surgery on the study hand (minimum interval, 2.5 months), and 1 had not pursued surgery on the study hand.

Primary End Points
Symptom Severity at 10 Weeks

The baseline CTS symptom severity score at 10 weeks improved more in patients who received methylprednisolone than those who received placebo ($P = 0.003$ for 80 mg and $P < 0.001$ for 40 mg of methylprednisolone) (Table 2). The mean change in score from baseline to 10 weeks was $-0.90$ (SD, 1.0) in the 80-mg methylprednisolone group, $-1.17$ (SD, 0.95) in the 40-mg methylprednisolone group, and $-0.30$ (SD, 0.66) in the placebo group. The mean difference in change from baseline to 10 weeks was $-0.64$ (CI, $-1.06$ to $-0.21$) between the 80-mg methylprednisolone and placebo groups and $-0.88$ (CI, $-1.30$ to $-0.46$) between the 40-mg methylprednisolone, 40 mg ($n = 37$)
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nisolone and placebo groups. No significant difference in score change was found between the 80- and 40-mg methylprednisolone groups (mean difference, 0.24 [CI, −0.20 to 0.69]).

At the 10-week follow-up, patients in all groups who decided to pursue surgery by 3 months had worse 10-week symptom severity scores than patients who did not pursue surgery (mean score, 2.98 [SD, 0.77] vs. 1.56 [SD, 0.72]; mean score change from baseline, −0.23 vs. −1.38; mean difference in score change, 1.15 [CI, 0.86 to 1.44]).

Rate of Surgery at 1 Year

At 1 year, 73%, 81%, and 92% of patients had surgery in the 80-mg methylprednisolone, 40-mg methylprednisolone, and placebo groups, respectively. Compared with patients who received placebo, those who received 80 mg of methylprednisolone had a lower likelihood of having surgery within 1 year after injection (odds ratio, 0.24 [CI, 0.06 to 0.95]; \( P = 0.042 \)), but no significant difference was found between the 40-mg methylprednisolone and placebo groups or between the methylprednisolone groups (Table 2). Cox regression analysis with constant time showed that the relative risk for surgery within 1 year (compared with placebo) was 0.79 (CI, 0.64 to 0.99; \( P = 0.039 \)) for the 80-mg methylprednisolone group and 0.88 (CI, 0.73 to 1.06; \( P = 0.180 \)) for the 40-mg methylprednisolone group.

Secondary End Points

Time from injection to surgery was longer for the 80-mg methylprednisolone group (\( P = 0.003 \)) and 40-mg methylprednisolone group (\( P = 0.022 \)) than the placebo group (Figure 2). In the Cox regression analysis, patients

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**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methylprednisolone, 80 mg (n = 37)</th>
<th>Methylprednisolone, 40 mg (n = 37)</th>
<th>Placebo (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD), y</td>
<td>47 (12)</td>
<td>44 (11)</td>
<td>49 (11)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>26 (70)</td>
<td>27 (73)</td>
<td>28 (76)</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>26.7 (4.9)</td>
<td>28.9 (7.1)</td>
<td>27.5 (5.5)</td>
</tr>
<tr>
<td>Dominant hand treated, n (%)</td>
<td>30 (81)</td>
<td>30 (81)</td>
<td>28 (76)</td>
</tr>
<tr>
<td>Duration of symptoms, n (%)</td>
<td>34 (92)</td>
<td>27 (73)</td>
<td>32 (87)</td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>3 (8)</td>
<td>10 (27)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Employed, n (%)</td>
<td>32 (87)</td>
<td>33 (89)</td>
<td>32 (87)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>8 (22)</td>
<td>12 (32)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>Alcohol consumption, n (%)†</td>
<td>4 (11)</td>
<td>5 (14)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>1–9 drinks/wk</td>
<td>31 (84)</td>
<td>28 (76)</td>
<td>29 (78)</td>
</tr>
<tr>
<td>≥10 drinks/wk</td>
<td>5 (14)</td>
<td>4 (11)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Positive Phalen test results, n (%)</td>
<td>34 (92)</td>
<td>36 (97)</td>
<td>36 (97)</td>
</tr>
<tr>
<td>Positive Tinel test results, n (%)</td>
<td>19 (51)</td>
<td>19 (51)</td>
<td>23 (62)</td>
</tr>
<tr>
<td>Mean monofilament sensation (SD)‡</td>
<td>2.5 (0.7)</td>
<td>2.3 (0.8)</td>
<td>2.3 (0.8)</td>
</tr>
<tr>
<td>Mean 2-point discrimination (SD), mm‡</td>
<td>4.7 (1.0)</td>
<td>4.4 (0.8)</td>
<td>4.7 (1.0)</td>
</tr>
<tr>
<td>2-point discrimination, n (%)§</td>
<td>18 (49)</td>
<td>24 (65)</td>
<td>19 (51)</td>
</tr>
<tr>
<td>Mean grip strength (SD), kg</td>
<td>32 (17)</td>
<td>33 (16)</td>
<td>31 (15)</td>
</tr>
<tr>
<td>Mean pinch strength (SD), kg</td>
<td>5.1 (3.0)</td>
<td>5.8 (2.8)</td>
<td>5.3 (2.9)</td>
</tr>
<tr>
<td>Nerve conduction tests</td>
<td>Median ulnar sensory latency difference</td>
<td>Mean time (SD), ms</td>
<td>1.7 (0.8)</td>
</tr>
<tr>
<td></td>
<td>Mean patient-reported outcome measures (SD)¶</td>
<td>Mean CTS symptom severity score</td>
<td>2.93 (0.85)</td>
</tr>
<tr>
<td></td>
<td>QuickDASH score</td>
<td>39.9 (22.9)</td>
<td>40.8 (19.2)</td>
</tr>
<tr>
<td></td>
<td>SF-36 bodily pain score</td>
<td>45.1 (22.6)</td>
<td>43.5 (20.2)</td>
</tr>
<tr>
<td></td>
<td>SF-6D score</td>
<td>0.71 (0.14)</td>
<td>0.69 (0.13)</td>
</tr>
</tbody>
</table>

BMI = body mass index; CTS = carpal tunnel syndrome; QuickDASH = short Disabilities of the Arm, Shoulder and Hand; SF-36 = Short Form-36 Health Survey; SF-6D = Short Form-6D.

† A standard drink corresponds to 15 cl. of wine, 33 cl. of strong beer, or 4 cl. of spirits.
‡ Sensation in the thumb, index finger, middle finger, and radial half of the ring finger, using 5 monofilaments of increasing diameter, 1 (best) to 5, and 2-point discrimination starting from 4 mm (best).
§ Patients with 2-point discrimination values of 4 mm in all or 6 mm or ≥8 mm in at least 1 of the thumb, index finger, middle finger, and radial half of the ring finger.
¶ Peak sensory latency from the wrist to the index finger and from the wrist to the ring finger. Sensory response was absent in 5, 1, and 3 patients in the 80-mg methylprednisolone, 40-mg methylprednisolone, and placebo groups, respectively. Absent response or sensory latency difference ≥1.7 ms was considered severe, 1.0–1.6 ms was moderate, and 0.6–0.9 ms was mild.
¶‡ Symptoms severity, 1 (no symptoms) to 5 (most severe); QuickDASH, 0 (no disability) to 100 (most severe); SF-36 bodily pain, 0 (worst) to 100 (best); SF-6D, 0.30 (worst health state) to 1.0 (perfect health).
who received methylprednisolone had a lower likelihood of undergoing surgery than those who received placebo. The hazard ratios were 0.46 (CI, 0.27 to 0.77; \( P = 0.003 \)) for the 80-mg methylprednisolone group and 0.57 (CI, 0.35 to 0.94; \( P = 0.026 \)) for the 40-mg methylprednisolone group. No difference was found between the 80- and 40-mg methylprednisolone groups (hazard ratio, 0.81 [CI, 0.48 to 1.36]; \( P = 0.42 \)).

At 10 weeks, both methylprednisolone groups had greater improvement than the placebo group in Quick-DASH, SF-36 bodily pain, and SF-6D scores and higher treatment satisfaction (all \( P < 0.025 \)) (Table 3). At 24 weeks and 1 year, there were no differences between methylprednisolone and placebo in these outcomes (all \( P > 0.100 \)). No differences were found between the 80- and 40-mg methylprednisolone groups in any secondary end point (all \( P > 0.100 \)).

### Safety End Points

Pain after injection was reported by 24 patients in each methylprednisolone group and 6 patients in the placebo group (\( P = 0.001 \)). Pain was mild or moderate in most patients, and median duration was 2 days. Local swelling was reported by 10 patients (4 in each methylprednisolone group and 2 in the placebo group). In all patients, the pain or swelling had resolved within 2 weeks. No serious AEs occurred.

### Exploratory Analyses

#### Subgroup Analyses

Because of the relatively small number of patients in the prespecified subgroups and absence of a dose–response relationship, we combined patients who received methylprednisolone into 1 group. The effect of methylprednisolone on symptom severity was larger in patients with higher nerve conduction abnormality and baseline symptom severity (Appendix Table 1, available at www.annals.org).

#### Strength and Sensation

At 10 weeks, patients who received 80 mg of methylprednisolone had greater improvement in pinch strength (\( P = 0.044 \)) and monofilament sensation (\( P = 0.010 \)) than those who received placebo, but no other comparisons were significant (all \( P > 0.100 \)) (Appendix Table 2, available at www.annals.org). At 1 year, no between-group differences were found (all \( P > 0.20 \)).

### Discussion

This randomized, placebo-controlled trial of patients with idiopathic CTS shows a large and statistically significant benefit of first-time local methylprednisolone injection with regard to symptom improvement at 10 weeks but only a modestly lower likelihood of surgery within 1 year after treatment. The difference between methylprednisolone and placebo in symptom improvement at 10 weeks was

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**Table 2. Primary End Points**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Methylprednisolone Dose</th>
<th>Placebo</th>
<th>Mean Difference* or OR† (95% CI) and ( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change in CTS symptom severity score at 10 wk (SD)‡</td>
<td>80 mg</td>
<td>40 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td>Mean</td>
<td>(-0.90 (1.0))</td>
<td>(-1.17 (0.95))</td>
<td>(-0.30 (0.66))</td>
</tr>
<tr>
<td>Rate of surgery at 1 y, n (%)</td>
<td>27 (73)</td>
<td>30 (81)</td>
<td>34 (92)</td>
</tr>
<tr>
<td>Mean difference in CTS</td>
<td>(-0.64 (\text{CI} = -1.06 \text{ to } -0.21))</td>
<td>(-0.88 (\text{CI} = -1.30 \text{ to } -0.46))</td>
<td>(0.24 (\text{CI} = 0.02 \text{ to } 0.69))</td>
</tr>
<tr>
<td>( P = 0.003 )</td>
<td>( P &lt; 0.001 )</td>
<td>( P = 0.29 )</td>
<td></td>
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</tbody>
</table>

CTS = carpal tunnel syndrome; OR = odds ratio.

* Mixed-model analysis for difference between treatment groups in score change from baseline to 10 wk, adjusting for the baseline score.

† OR, derived from logistic regression, of having surgery within 1 y after treatment.

‡ CTS symptom severity score range, 1 (no symptoms) to 5 (most severe).
A systematic review of steroid injection in CTS (7) found 2 good-quality, double-blind, placebo-controlled trials, and we found only 1 similar recent trial; none remained blinded beyond 1 month. One trial (81 patients) reported better patient satisfaction 2 weeks after patients received 6 mg of betamethasone (8), and another trial (60 patients) reported better symptomatic improvement 1 month after patients received 40 mg of methylprednisolone (9). In the third trial (20), 35 patients received 10 mg of triamcinolone (24 received 2 injections in 1-week intervals), and 31 patients received saline. At 3 weeks after injection (blinding was terminated), the triamcinolone group had a larger improvement in the CTS symptom severity score than the saline group (mean difference, −0.64).

One limitation of our study is that it was done at 1 center. However, it is the only referral center for patients with CTS in a region where primary care physicians do not use steroid injections. Thus, the results could be generalizable to patients who were unsuccessfully treated with wrist splinting. That patients were considered for surgery should not imply that the findings apply only to more severe CTS. First, patients with muscle atrophy and severe sensory deficit were ineligible. Second, the subgroup analyses showed that the benefit of methylprednisolone was in fact larger in patients with higher nerve conduction abnormality and

weeks is clinically important, corresponding to a moderate to large effect size (19). The effect is not influenced by surgery because only 2% of the patients had surgery at 10 weeks. However, most patients required surgery within 1 year after injection, indicating that the effect is often not durable. Patients who received 80 mg of methylprednisolone had a modest but statistically significant lower likelihood of requiring surgery within 1 year than those who received placebo. It is uncertain whether this relatively small difference could justify steroid injection as routine treatment of idiopathic CTS. However, considering the large number of surgical procedures (2), even a small reduction may be valuable. Besides the lower rate of surgery, the methylprednisolone group obtained similar 1-year symptoms, function, and quality-of-life outcomes as the placebo group, indicating no substantial residual symptoms.

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symptom severity. Another potential limitation is that patients could choose surgery at 3 months after randomization if they believed that their symptoms had not improved after injection. Before inclusion, all patients had been unsuccessfully treated with wrist splinting for at least 2 months. Because surgery is the only remaining treatment option with established efficacy (21), there was no acceptable alternative to offering surgery if the intervention failed. The data showed that patients who decided to pursue surgery had worse 10-week symptom severity scores than patients who did not pursue surgery, which supports our belief that patients’ decisions to choose surgery were based on persistent symptoms.

We did not find a significant difference between the 40- and 80-mg methylprednisolone groups for any end point and thus found no dose–response relationship. Although the prespecified logistic regression of rate of surgery only showed statistically significant difference from placebo for the 80-mg methylprednisolone group, Cox regression (which incorporates time to surgery) also showed a statistically significant difference between the 40-mg methylprednisolone group and placebo. When the event rate is high, Cox regression estimates have better precision than logistic regression odds ratios (22).

We used the proximal approach for methylprednisolone injection. In a randomized study, the outcomes of proximal and distal approaches for steroid injection were similar (23).

After methylprednisolone injection, the mean CTS symptom severity score improved by −1.1 at 10 weeks from 3.0 at baseline. A previous study showed a −1.6 improvement from 3.1 at baseline 3 months after surgery (3). In a previous trial of surgery versus various nonsurgical treatments, the baseline symptom severity score (mean, 3.0) improved at 6 months by −0.9 in the surgery group (50 patients) and −0.6 in the nonsurgery group (54 patients) (24). A previous randomized study of surgery (80 patients) versus steroid injection (83 patients) reported a better outcome (at least 20% improvement in nocturnal paresthesia) after steroid injection at 3 months (25). A randomized study of surgery (25 patients) versus steroid injection (25 patients) using a 0–50-point symptom score reported a 15-point greater improvement after surgery at 20 weeks (26).

To our knowledge, this study is the first blinded, placebo-controlled trial of steroid injection for CTS with a 1-year follow-up. It shows that methylprednisolone reduces symptoms and rate of surgery, but 3 of 4 patients still had surgery within 1 year. Future research should explore how to obtain a consistent durable effect. The goal is to find a medical treatment that effectively resolves CTS without the need to divide the transverse carpal ligament.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-3608.

Reproducible Research Statement: Study protocol: Available from Dr. Atroshi (e-mail, Isam.Atroshi@skane.se). Statistical code: Available from Professor Ranstam (e-mail, jonas.ranstam@med.lu.se). Data set: Request for data can be submitted to Dr. Atroshi (e-mail, Isam.Atroshi@skane.se).

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Current author addresses and author contributions are available at www.annals.org.

References


Hand Strength and Sensation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Methylenprednisolone*†</th>
<th>Placebo*</th>
<th>Difference in Score Change (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of symptoms</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1 y</td>
<td>−1.02 (0.97)</td>
<td>−0.22 (0.66)</td>
<td>−0.81 (−1.20 to −0.43)</td>
</tr>
<tr>
<td>≤1 y</td>
<td>−1.19 (1.0)</td>
<td>−0.78 (0.53)</td>
<td>−0.41 (−1.51 to 0.69)</td>
</tr>
<tr>
<td><strong>Nerve conduction tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately or severely abnormal</td>
<td>−1.16 (0.97)</td>
<td>−0.31 (0.70)</td>
<td>−0.87 (−1.25 to −0.48)</td>
</tr>
<tr>
<td>Normal or mildly abnormal</td>
<td>−0.49 (0.85)</td>
<td>−0.23 (0.54)</td>
<td>−0.26 (−1.26 to 0.75)</td>
</tr>
<tr>
<td><strong>Baseline CTS symptom severity score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3.0</td>
<td>−1.33 (1.06)</td>
<td>−0.30 (0.72)</td>
<td>−1.02 (−1.54 to −0.51)</td>
</tr>
<tr>
<td>&lt;3.0</td>
<td>−0.68 (0.71)</td>
<td>−0.29 (0.62)</td>
<td>−0.38 (−0.82 to 0.06)</td>
</tr>
</tbody>
</table>

CTS = carpal tunnel syndrome.
* Values are mean (SD) changes from baseline.
† Patients who received methylprednisolone were combined into 1 group because of the relatively small number of patients in the prespecified subgroups.
‡ Mixed-model analysis of change in symptom severity score from baseline to 10 wk, adjusting for the baseline score.

Appendix Table 2. Hand Strength and Sensation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change From Baseline*</th>
<th>Mean Difference in Change (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Methylenprednisolone, 80 mg</td>
<td>Methylenprednisolone, 40 mg</td>
</tr>
<tr>
<td><strong>Grip‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 wk</td>
<td>2.8 (4.1)</td>
<td>2.3 (4.4)</td>
</tr>
<tr>
<td>1 y</td>
<td>1.9 (7.5)</td>
<td>1.6 (8.7)</td>
</tr>
</tbody>
</table>

| **Pinch‡**        |                       |                                   |          |                                        |                                    |                                      |
| 10 wk             | 1.2 (1.1)             | 0.7 (1.5)                         | 0.3 (1.4) | 1.0 (0.2 to 1.7)                      | 0.4 (−0.3 to 1.2)                  | 0.5 (−0.2 to 1.2)                   |
| 1 y               | 1.5 (1.8)             | 1.3 (1.9)                         | 1.1 (1.5) | 0.5 (−0.2 to 1.2)                     | 0.2 (−0.5 to 0.9)                  | 0.2 (−0.5 to 1.0)                   |

| **Monofilament**  |                       |                                   |          |                                        |                                    |                                      |
| 10 wk             | −0.27 (0.5)           | −0.16 (0.9)                       | 0.13 (0.7) | −0.35 (−0.68 to −0.01)                 | −0.25 (−0.59 to 0.08)              | −0.10 (−0.45 to 0.26)               |
| 1 y               | −0.38 (0.8)           | −0.44 (0.8)                       | −0.26 (0.5) | −0.11 (−0.44 to 0.22)                 | −0.17 (−0.50 to 0.16)              | 0.06 (−0.29 to 0.41)               |

| **2-point discrimination** |                       |                                   |          |                                        |                                    |                                      |
| 10 wk             | −0.07 (1.5)           | −0.06 (1.0)                       | 0.02 (0.9) | −0.06 (−0.53 to 0.41)                 | −0.06 (−0.52 to 0.41)              | 0.003 (−0.47 to 0.47)               |
| 1 y               | −0.34 (0.7)           | −0.26 (0.9)                       | −0.47 (0.9) | 0.13 (−0.33 to 0.59)                 | 0.22 (−0.25 to 0.68)              | −0.09 (−0.55 to 0.38)               |

* Values are means (SDs).
† Mixed-model analysis for difference in change over time between groups, adjusting for the baseline value. Values in bold indicate statistical significance.
‡ Measured with the Jamar Hand Dynamometer (Sammons Preston, Bolingbrook, Illinois) and the Exacta Pinch Gauge (North Coast Medical, Gilroy, California); average values of 3 trials recorded.