PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Costs of collagenase injections compared with fasciectomy in the treatment of Dupuytren's contracture: A retrospective cohort study
AUTHORS	Atroshi, Isam; Strandberg, Emelie; Lauritzson, Anna; Ahlgren, Eva; Waldén, Markus

VERSION 1 - REVIEW

REVIEWER	Shaunak Desai, MD. Newport Orthopedic Institute Newport Beach, CA United States of America
REVIEW RETURNED	27-Oct-2013

GENERAL COMMENTS	The number of patients in each group could be higher. Although the authors have performed a Power analysis to generate this number, more potential complications could be discovered with a larger group of patients. This could change the cost analysis. The authors should be commended on their concise and organized study analyzing the cost effectiveness of collagenase injections vs surgery at their institution. Overall, they have provided adequate data to support their hypothesis that collagenase injections are more cost-effective than standard surgery in the short term. They do mention multiple times that cost to vary from country to country. It should be noted that the price of a single collagenase injection in the United States is currently a little over US $3,000. This cost analysis may not readily be extrapolated to other countries when their is such large differences in healthcare costs.

REVIEWER	Prof Jagdeep Nanchahal Kennedy Institute of Rheumatology Nuffield Dept of Orthopaedics, Rheumatology and Musculoskeletal Sciences University of Oxford UK
REVIEW RETURNED	01-Nov-2013

GENERAL COMMENTS	This is a nicely written paper that addresses an important question - cost efficacy of a common hand disorder. Title + Abstract: I think the authors should make clear that this was a retrospective analysis. Under participants in the abstracts I think it should read 30 degrees or greater at the MCPJ AND/OR PIPJ Under conclusions they should define that the 'short-term' was 6

	weeks Introduction: 2nd paragraph - the authors state that the patients treated with CCH received one injection per digit. In the publication by Hurst (NEJM 2009) each patient required a mean of just over 2 injects per digit to achieve a correction to within 5 degrees of neutral. Therefore, the present study was not aimed at achieving the maximal correction, but instead what correction could be achieved with one injection. This needs to be clarified as if every patient received 2 injections of CCH at c$1000 each, then surgery becomes the cheaper option. Results: There were differences in the follow up of the 2 groups - 5-6wk for CCH with a therapist and 3 months for surgery with a surgeon + nurse. The final appointment in the latter group will be more expensive in terms of personnel costs. Table 1: the PIPJ and MCPJs flexion deformities should be listed separately in addition to the aggregate flexion contraction. This is important as the PIPJs are less likely to achieve correction with surgery and especially with CCH. Also, was the PIPJ flexion fixed i.e. could it be corrected with MCPJ flexion pre-operatively? These patients are likely to achieve complete correction. Also, were all the cords pre-tendinous? These are likely to respond to both CCH or surgery whereas spiral cords are less amenable to CCH treatment and one could argue are best addressed surgically and hence the 2 groups of patients are not exactly comparable. Table 3: Again the data for PIPJ and MCPJ should be presented separately. The differences in follow up for the 2 groups is somewhat problematic as patients undergoing surgery may initially (3-6 wk) have a better correction than at 3 months, especially at the PIPJ level. Discussion: First sentence - they emphasise that 5-6 weeks is very short follow up. Also, should detail differences in their single CCH injection technique as opposed to the protocol in Hurst et al where the patient received up to 2 injections to achieve max correction. The cost of an additional injection would reverse their conclusion. Page 15 - the comparative costs of carpal tunnel surgery in Canada are irrelevant. I would prefer to see costs for Dup surgery in US. Page 16 - the authors have misquoted the Peimer paper (2013). The follow up of the CCH patients was for 3 years not 5 years. Also, the global recurrence rate of 35% is misleading - it was 27% for MCPJ but much higher at 56% for PIPJ. Clearly the aggregate of 35% depends of the relative proportion of each type of joint. The authors should add for comparison the 3 year recurrence data for surgical fasciectomy - 10% (van Rijssen et al 2012) and 12% Ullah et al (2009). So in the long term, it is possible that CCH is less cost effective - this needs to be emphasised in the discussion.

VERSION 1 – AUTHOR RESPONSE

Response to review by Dr Shaunak Desai, MD

Although the authors clearly provide a mean Total Extension Deficit (TED), it would help to know how much contracture was related to the MPJ vs PIPJ. How many in each group was related to primary MPJ contracture vs. PIPJ contracture. It is clear that PIPJ contracture fair worse with treatment than MPJ contracture. It would be helpful to know, if both groups were similar in make-up.

We have added data about MCP and PIP joint contractures separately (Tables 1 and 3), which shows that the groups were generally similar in this respect.

The number of patients in each group could be higher. Although the authors have performed a Power analysis to generate this number, more potential complications could be discovered with a larger group of patients. This could change the cost analysis.

Although a larger sample size is often preferable it would not have affected the cost comparison as clarified in the "Analysis" section (Pages 10-11). As we have also mentioned in the Discussion (Lines 281-284), our study estimated the direct costs that did not include the cost of possible complications (there were no complications in any group). Generally, the rate of serious complications for both treatments is relatively low but it may probably be higher after surgery (such as wound complications, chronic regional pain syndrome, and nerve injury). With regard to the comparison of short-term outcomes we based our sample size estimation on the data reported in two high-quality randomized trials (lines 216-218).

The authors should be commended on their concise and organized study analyzing the cost effectiveness of collagenase injections vs surgery at their institution. Overall, they have provided adequate data to support their hypothesis that collagenase injections are more cost-effective than standard surgery in the short term. They do mention multiple times that cost to vary from country to country. It should be noted that the price of a single collagenase injection in the United States is currently a little over US $3,000. This cost analysis may not readily be extrapolated to other countries when their is such large differences in healthcare costs.

Thank you. We agree that the costs may vary in different countries, which we already have emphasized (Line 52). We have added a comment about the higher cost of the injection in some countries (Lines 323-328).

Response to review by Prof Jagdeep Nanchahal

This is a nicely written paper that addresses an important question - cost efficacy of a common hand disorder.

Title + Abstract:
I think the authors should make clear that this was a retrospective analysis.

We have clarified this in the title and abstract. Although we now describe the study design in the title "retrospective", as requested, we wish to emphasize that the study is only partly retrospective because, as described in the manuscript, the data collection for the surgery group was retrospective but that for the injections group was prospective.

Under participants in the abstracts I think it should read 30 degrees or greater at the MCPJ AND/OR PIPJ Under conclusions they should define that the 'short-term' was 6 weeks

As requested these changes have been done in the abstract (Lines 25, 43).

Introduction:
2nd paragraph - the authors state that the patients treated with CCH received one injection per digit. In the publication by Hurst (NEJM 2009) each patient required a mean of just over 2 injects per digit to achieve a correction to within 5 degrees of neutral. Therefore, the present study was not aimed at achieving the maximal correction, but instead what correction could be achieved with one injection. This needs to be clarified as if every patient received 2 injections of CCH at c$1000 each, then surgery becomes the cheaper option.

We believe there are 2 possible explanations as to why fewer injections were needed in our study than in the study by Hurst et al. (NEJM 2009). First, in the study by Hurst et al. finger manipulation (extension), which is often a painful procedure, was done without anaesthesia; this may have reduced the degree of initial contracture correction, necessitating a second injection. We performed finger manipulation under local anaesthesia in all our patients. To our knowledge, almost all physicians who use CCH now routinely give local anaesthesia before finger extension. The second factor that may have reduced the need for repeat injection is that Hurst et al. injected 0.58 mg CCH into one part of the cord but we use a modified injection technique, in which we inject the whole content of each CCH injection (0.9 mg) into multiple sites in the cord. We have now described the technique used (Lines 130-134).
Besides, if a patient is satisfied with the degree of contracture correction despite not reaching within 5 degrees of neutral it would not be reasonable to ask the patient to have a second injection to reach that level. Even Hurst et al. (2009) stated that “More than half of the collagenase-treated joints that did not meet the primary end point did not receive the maximum allowable number of collagenase injections (three per cord), most commonly because investigators could not palpate a cord or patients were satisfied with the result.” We have added a clarification about this issue (Line 140-142). Our results show that good correction can be achieved with a single injection.

Results:
There were differences in the follow up of the 2 groups - 5-6wk for CCH with a therapist and 3 months for surgery with a surgeon + nurse. The final appointment in the latter group will be more expensive in terms of personnel costs.

The final appointment for the surgery patients was done because orthopaedic and hand surgeons usually want to see their patients after this type of non-minor surgery. However, as seen in Table 2, the cost of this visit is relatively small in relation to the total cost of surgery and excluding this final visit would not substantially change the cost comparison.

Table 1:
the PIPJ and MCPJs flexion deformities should be listed separately in addition to the aggregate flexion contraction. This is important as the PIPJs are less likely to achieve correction with surgery and especially with CCH. Also, was the PIPJ flexion fixed i.e. could it be corrected with MCPJ flexion pre-operatively? These patients are likely to achieve complete correction. Also, were all the cords pre-tendinous? These are likely to respond to both CCH or surgery whereas spiral cords are less

amenable to CCH treatment and one could argue are best addressed surgically and hence the 2 groups of patients are not exactly comparable.

We have added data regarding separate PIP and MCP joint contractures to Table 1, which shows that the groups were generally similar in this respect. For the separate PIP and MCP contractures we have calculated the values only for joints that had contracture before treatment, which better reflects the severity of contracture; we have clarified this in the footnote. Including all joints (even those with no contracture before treatment) will give in both groups similarly lower mean and median contracture values, especially for the PIP (we can add these values if desired).
Because data for the surgery group were retrospective, information about whether the PIP contracture was fixed or whether the cord was pretendinous or spiral was not regularly recorded. These criteria were not used for choosing the treatment method in this study but, as we have stated, the indications for CCH were the same as for surgery (a palpable cord and contracture of MCP and/or PIP joint of 30 degrees or greater). It is possible that the response to surgery or CCH may differ according to type of cord but to our knowledge there are currently no studies that have addressed that issue.

Table 3:
Again the data for PIPJ and MCPJ should be presented separately. The differences in follow up for the 2 groups is somewhat problematic as patients undergoing surgery may initially (3-6 wk) have a better correction than at 3 months, especially at the PIPJ level.

We have added the data for the PIP and MCP joints separately in Table 3.
We agree that following surgery patients may have better PIP correction at 3-6 weeks than at 3 months, but for the patients in this study the length of follow-up after surgery depended on the length of therapy needed. Thus, surgery patients who had a longer follow-up than 5-6 weeks did not have adequate correction at that time and the therapist judged that they might improve further with continued therapy and therefore the follow-up was up to 3 months. This might in fact have favoured the surgery group.

Discussion:
First sentence - they emphasise that 5-6 weeks is very short follow up. Also, should detail differences in their single CCH injection technique as opposed to the protocol in Hurst et al where the patient received up to 2 injections to achieve max correction. The cost of an additional injection would reverse their conclusion.

We have emphasized the short follow-up (Lines 275, 330).
We have done the sensitivity analysis calculating the cost assuming 20% of the patients are treated with 2 injections. As we mentioned in the Discussion (Line 276-278), the direct costs of CCH would exceed those of surgery when more than 50% of the patients require 2 injections. We have clarified the possible explanations regarding the need for fewer injections, namely routinely using local anaesthesia before finger manipulation and a modified injection technique (injecting the whole content of a single CCH injection into multiple sites in the cord) (Lines 284-291).

Page 15 - the comparative costs of carpal tunnel surgery in Canada are irrelevant. I would prefer to see costs for Dup surgery in US.

We cited the costs of carpal tunnel surgery as an example that even in the same country the actual direct costs of a surgical procedure may vary depending on the setting in which the procedure is performed (office versus hospital). Despite our search we could not find a study reporting the actual

direct costs of surgery in the US. We have now cited the study from the US that reported the reimbursement for fasciectomy, which of course is not the same as actual costs (Lines 323-328).

Page 16 - the authors have misquoted the Peimer paper (2013). The follow up of the CCH patients was for 3 years not 5 years. Also, the global recurrence rate of 35% is misleading - it was 27% for MCPJ but much higher at 56% for PIPJ. Clearly the aggregate of 35% depends of the relative proportion of each type of joint.

We apologize for this citation error which we have now corrected to 3 years follow-up and added the joint-specific recurrence rates (Line 334-338).

The authors should add for comparison the 3 year recurrence data for surgical fasciectomy - 10% (van Rijssen et al 2012) and 12% Ullah et al (2009).

We have added this information (Lines 338-342). Our interpretation of the data provided in the study by Van Rijssen et al. (2012) is that the recurrence rate was 12%, derived from the following statements in their article: “During 5-year follow-up, 33 hands in 31 patients treated with limited fasciectomy did not develop recurrence (76.8 percent), whereas nine hands did (20.9 percent). One hand showed extension (2.3 percent). ….. For limited fasciectomy, there were two recurrences at 2 years, two at 3 years, three at 4 years, and three at 5 years.” Thus, 4 recurrences up to 3 years in 33 hands yield a 12% recurrence rate.

So in the long term, it is possible that CCH is less cost effective - this needs to be emphasised in the discussion.

We agree that this is possible and have mentioned this in the Discussion (Lines 342-345); we have compared the current costs and the short-term outcomes. As for all new treatment methods, costs will need to be reassessed when long-term outcomes become available, specifically the proportion of patients who would subsequently need further treatment.