PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Outcome of Surgical Repair of Adult Digital Nerve Injury: A Systematic Review
AUTHORS	Dunlop, Rebecca; Wormald, Justin; Jain, Abhilash

VERSION 1 - REVIEW

REVIEWER	Professor Hamid Karimi Professor of Plastic, Reconstructive and Aesthetic Surgery Iran University of Medical Sciences, Tehran, Iran
REVIEW RETURNED	03-Sep-2018

GENERAL COMMENTS	1. I have to congratulate the authors for performing such a complex and well-organized study. 2. The paper is well-written and informative about the design of study. 3. But there are some varieties in the date of researched papers (before and after magnification), type (mechanism and severity) of injuries, experience level of the surgeons, smoking and others. Therefore this study does not seem to be homologous. 4. Although only 30 papers met the inclusion criteria, it would be better to categorized them according to important variables such as date of papers, level of experience, delay in treatment (between 0 to 30 months delay is not a uniform group), suturing techniques and materials(silk or nylon), and type of injuries. 5. In this way , although your selected papers would be less than 30, but would be more precise and conclusive.(I don't think the results of treatments in 1920s would be very interesting for our readers, as we have passed a long time ago from that point and we have learned a lot after the surgeons in 1920s. For sure we will not do the same mistakes as in 1920s). 6. The results of 1920s or 1950s are not comparable with 2016s and cannot be gathered in one group. 7. The good and strong points in this paper that should be emphasized more are: measurements tools, adverse outcomes, techniques of repair and rehabilitation. 8. The proper paper is the one that compared the repair with non-repair. I think their results are reliable and should be more discussed. The limitation of that paper also can be emphasized. 9. It is better to add the "Modified Highet Classification" as a table. 10. I think the conclusion has to be written vice versa. Although there are not enough evidence for repairing the digital nerve, the only conclusive paper in this regard, stated that repair has better outcome! 11. The conclusion in abstract should be re-written too.

REVIEWER	Prof. Dr. Jörn A. Lohmeyer Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany
REVIEW RETURNED	10-Sep-2018

GENERAL COMMENTS	In the present literature evaluation, a comparison between direct nerve suture and lack of surgical care is to be made, although the data situation for cases of missing nerve suture is very weak. The authors' argument that the nerve suture is comparatively expensive and, therefore expendable against the background of the insufficient data available in the absence of a nerve suture. In my clinical an research experience, especially thumb and index finger nerves have to be sutured, because every additional chance to improve sensitivity should be preserved. With a good pair of magnifying glasses or a surgical microscope, it does not even com with a significant lengthening of the procedure. In comparison to a pure skin suture, there should be no need for in-patient treatment, even in the case of sick patients. The statement on the incidence of postoperative neuroma is based on a comparative study without nerve suture with an incidence of 2/39 patients. It is easy to see that a completely different percentage would have resulted if only one additional patient would have suffered from a neuroma. A valid statement on neuroma incidence in the absence of nerve reconstruction is therefore not possible on the basis of this data. The classification used with sole consideration of the Highet Grade 4 group is very unspecific and broad. Here, too, a valid comparison seems hardly possible, especially since, as already mentioned, a valid and sufficiently big comparison group is missing. The authors themselves emphasize that a better surgical experience goes hand in hand with a better return of sensitivity after the nerve suture. Thus, it also seems evident that the surgical care, if well performed, must have a positive effect. In addition, numerous included studies originate from a time in which, if at all, at most low optical magnification was used for suturing. And concerning the conclusion of the authors: “Until further evidence is demonstrated, we concur with A. Clarke, who writing his commentary of Fakin’s paper in 2016 wrote, “If I sustained a digital nerve injury, it is unlikely I would be seeking surgical repair” (Fakin et al., 2016) I would rather comment: The absence of evidence is not the evidence of absence. I consider a publication of this work with the resulting recommendation especially for young colleagues to be grossly negligent. The lack of care for peripheral nerve injury can harm those affected. In my opinion, a publication is therefore not to be recommended.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Professor Hamid Karimi

Institution and Country: Professor of Plastic, Reconstructive and Aesthetic Surgery, Iran University of Medical Sciences, Tehran, Iran

I have to congratulate the authors for performing such a complex and well-organized study.

Thank you Professor Karimi.

The paper is well-written and informative about the design of study.

Thank you.

But there are some varieties in the date of researched papers (before and after magnification), type (mechanism and severity) of injuries, experience level of the surgeons, smoking and others. Therefore, this study does not seem to be homologous.

Thank you. As per standard, rigorous systematic review methodology as described in the Cochrane Handbook of Systematic Reviews, all studies from database inception to November 2018 were included if they met our pre-defined inclusion criteria. We have made efforts to discuss the results of all of the studies in context of their publication dates. We agree that the studies are heterogeneous and this needs to be considered when designing future research on digital nerve repair.

Although only 30 papers met the inclusion criteria, it would be better to categorized them according to important variables such as date of papers, level of experience, delay in treatment (between 0 to 30 months delay is not a uniform group), suturing techniques and materials (silk or nylon), and type of injuries.

Thank you. We agree that the included papers are heterogeneous. Unfortunately, this simply reflects the nature of the body of literature on digital nerve repair. While we cannot tackle this issue in our review, we believe that this heterogeneity in the literature is an important finding.

In this way, although your selected papers would be less than 30, but would be more precise and conclusive (I don't think the results of treatments in 1920s would be very interesting for our readers, as we have passed a long time ago from that point and we have learned a lot after the surgeons in 1920s. For sure we will not do the same mistakes as in 1920s).

Please see response to comment 3. We do not want to compromise rigorous methodology.

The results of 1920s or 1950s are not comparable with 2016s and cannot be gathered in one group.

Please see response to comment 3 and 4.

The good and strong points in this paper that should be emphasized more are: measurements tools, adverse outcomes, techniques of repair and rehabilitation.

Thank you.

The proper paper is the one that compared the repair with non-repair. I think their results are reliable and should be more discussed. The limitation of that paper also can be emphasized.

This has been elaborated upon.

It is better to add the "Modified Highet Classification" as a table.

This has been included as a supplementary table.

I think the conclusion has to be written vice versa. Although there are not enough evidence for repairing the digital nerve, the only conclusive paper in this regard, stated that repair has better outcome!

This has been amended.

The conclusion in abstract should be re-written too.

This has been amended.

We thank Professor Karimi for his favourable review and hope that he is satisfied by our responses.

Reviewer 2: Prof. Dr. Jörn A. Lohmeyer

Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

In the present literature evaluation, a comparison between direct nerve suture and lack of surgical care is to be made, although the data situation for cases of missing nerve suture is very weak.

In response to your first statement, we would like to clarify that although we sought to compare the results of direct nerve suture with no repair, we in no way endorse 'lack of surgical care' for these patients. Surgical wound debridement and repair of other vital digital structures is of course mandatory in many cases and we do not seek to conflate non-repair of a damaged nerve with overall lack of surgical care. However, your point that the data is weak to justify no repair is valid but our review also clearly demonstrates that the data of outcome following repair is also of poor quality and demonstrates that only 24% of patients regain what can be considered "normal" sensation. In these studies the most frequent primary outcomes assessed were not patient reported, but involved clinical assessments of finger sensibility, assessed by spatial discrimination (2 point discrimination) and detection threshold. The former is subject to learning effects which can lead to inflated values and neither of these truly reflect the functional impact of sensory impairment. Furthermore, it is possible that the "excellent" results documented in these studies were related to repairs done in children, despite our stringent attempts to ensure children were excluded. Therefore, while we agree there is limited data to support the no-repair approach, there is currently equally weak data to support the repair of single digital nerves in adults.

The authors' argument that the nerve suture is comparatively expensive and, therefore expendable against the background of the insufficient data available in the absence of a nerve suture.

Although we have pointed out the cost of digital nerve repair as part of the introduction to this paper, we have neither stated nor directly implied that cost alone should be used as an argument against surgical nerve repair. Instead, we feel that the decision whether to repair a nerve or leave it unrepaired should be determined by the likely benefit or otherwise to the patient, which was what this review sought to elucidate. In response to your point however, despite the resources required for this surgical repair procedure there is limited evidence, with regards to patient reported outcomes measures or functional improvement, that surgical repair offers significant benefit to patients. Administering specific surgical treatment of unknown efficacy or value is problematic for both individual patient wellbeing and the health service. If surgical repair is not necessary, or less effective, than other forms of treatment then the practice should be changed. There may be risk of complications or unsatisfactory outcome for individual patients if inappropriate practice is continued. The implications for the healthcare system are twofold. Firstly there is a duty of care to only provide effective and beneficial treatment. Secondly, savings can be made by eliminating additional costs for specialist equipment and personnel for a treatment that may be unnecessary. A conservative estimate

of the cost of microsurgical repair of isolated digital nerve injuries in the UK is over £10 million a year. This does not take into account patient related costs and loss to the economy due to time off work. If surgical repair is necessary and beneficial then high quality evidence needs to be provided to substantiate its continued use. Conversely, if repair is unnecessary, treatment may be provided in the accident and emergency department (A&E) rather than formal, and expensive, referral to a specialist hand surgery unit.

In my clinical an research experience, especially thumb and index finger nerves have to be sutured, because every additional chance to improve sensitivity should be preserved. With a good pair of magnifying glasses or a surgical microscope, it does not even com with a significant lengthening of the procedure. In comparison to a pure skin suture, there should be no need for in-patient treatment, even in the case of sick patients.

We agree with you that nerve suture is a day case procedure even in sick patients and that magnification does not significantly lengthen the procedure duration.

You have stated “In my clinical and research experience, especially thumb and index finger nerves have to be sutured, because every additional chance to improve sensitivity should be preserved.” You will admit this is your personal experience but it is not supported in the literature by high quality evidence. Our systematic review is methodologically sound and provides a complete summary of the evidence along with an assessment of its quality. It is therefore an unbiased reflection of the entire body of knowledge of isolated digital nerve repair in adults and is not at risk of anecdotal or personal experience. Furthermore, this systematic review is the first stage of a larger piece of work currently being undertaken in the United Kingdom on the evidence for and against digital nerve repair. In 2016 the British Society for Surgery of the Hand (BSSH) funded a study to look at non-interventional / Placebo surgery in the UK and identified repair of digital nerves as a health resource topic to study. This was further confirmed in the BSSH funded James Lind Alliance Priority Setting Exercise published last year (http://www.jla.nihr.ac.uk/priority-setting-partnerships/common-conditons-affecting-the-hand-and-wrist/). Furthermore, the National institute of Health Research (NIHR) undertook an independent review of the data in 2017 for the evidence to repair a digital nerve and came to the same conclusion we have in that there is no strong evidence to support it. They commissioned a trial to compare no repair with repair of digital nerves in April this year (reference 18/37 NIHR127807 – 18/37 - Repair of digital nerve injury).

Our group has responded to this call and have undertaken surgeon and patient surveys across the UK. We have engaged clinical stakeholders at every stage of our preliminary work. The work has been presented to an expert group of 25 consultant nerve surgeons in Birmingham (April 2018). Subsequently, a nationwide survey of all members of the British Association of Plastic Surgeons (BAPRAS), Hand Surgeons (BSSH), British Association of Hand Therapists (BAHT) and Reconstructive Surgery Trials Network (RSTN) has been conducted to gauge opinion on digital nerve repair surgery and guide trial design. Responses from our survey of over 100 surgeons and therapists confirmed the uncertainty and existence of community equipoise. Approximately half of respondents agree with you and stated that microsurgical repair is effective and essential. In particular those surgeons involved in commercial nerve conduit work/research were particularly vocal against a no-repair approach as it had financial implications if suggestion was made that digital nerve repair was deemed less effective than currently thought. However, a considerable number of surgeons were uncertain of efficacy of surgery and confirmed the need and willingness to engage with such a trial. So while we respect your opinion it is not a view shared by every surgeon and is not based on high quality evidence. The diversity in belief and in current practices between surgeons will be considered in the development of a trial protocol.

The statement on the incidence of postoperative neuroma is based on a comparative study without nerve suture with an incidence of 2/39 patients. It is easy to see that a completely different percentage would have resulted if only one additional patient would have suffered from a neuroma. A

valid statement on neuroma incidence in the absence of nerve reconstruction is therefore not possible on the basis of this data.

We agree that the pooled incidence of neuroma could easily be altered markedly by just a few patient difference. This is because of the inherently high fragility index of the (level IV) evidence available. However, the data published is all we have available on which to make a statement on. We could all also argue that if the repaired group had more patients with neuroma then that incidence could also go up. The fact of the matter is the data we have reported is what is published and all that any of us can draw conclusion from and therefore needs to be presented in an accurate way. The pooled data currently does not support the view of some surgeons that neuroma rates are higher if a digital nerve is not repaired and therefore cannot be used as justification to continue to repair a nerve.

The classification used with sole consideration of the Highet Grade 4 group is very unspecific and broad. Here, too, a valid comparison seems hardly possible, especially since, as already mentioned, a valid and sufficiently big comparison group is missing. The authors themselves emphasize that a better surgical experience goes hand in hand with a better return of sensitivity after the nerve suture. Thus, it also seems evident that the surgical care, if well performed, must have a positive effect. In addition, numerous included studies originate from a time in which, if at all, at most low optical magnification was used for suturing.

The reason that we chose Highet Grade 4 as the primary outcome is that it was the most frequently reported across papers and best approximates the return of normal sensation and is therefore the most desirable and meaningful result following any intervention. However, we accept it has its limitations. We felt that Highet Grades S1 –S3+, where s2PD could be as low as 7mm, potentially represented minimal achievement, in particular since no papers measured pre-operative s2PD for comparison. We did report that this review suggests a correlation between greater surgical experience and better s2PD outcomes, but since all the available evidence was Level IV at best, we felt that it was inappropriate to draw further on this conclusion.

Only two out of the 30 papers included in our review expressly did not use magnification and only one further paper was published before 1965, when in your own paper you state that magnification became generally available. None of these three papers influenced our s2PD results since none reported s2PD outcomes with enough clarity or detail to be included in our analysis. Therefore, although these papers are included in the systematic review for completeness, we would like to reassure you that their inclusion does not in any way change the outcome of our findings or conclusions.

And concerning the conclusion of the authors: “Until further evidence is demonstrated, we concur with A. Clarke, who writing his commentary of Fakin’s paper in 2016 wrote, “If I sustained a digital nerve injury, it is unlikely I would be seeking surgical repair” (Fakin et al., 2016) I would rather comment: The absence of evidence is not the evidence of absence.

We have removed this and other similar comments from the paper to convey the more objective message from our paper.

I consider a publication of this work with the resulting recommendation especially for young colleagues to be grossly negligent. The lack of care for peripheral nerve injury can harm those affected. In my opinion, a publication is therefore not to be recommended.

While we respect your personal opinion it is not a viewed shared by all surgeons. In fact reviewer one disagrees with you, as does the British Society for Surgery of the Hand, National Institute of Health Research and 50% of Hand Surgeons in the United Kingdom based on our national survey. Indeed just last month (October 2018) at the National BSSH Scientific Meeting in London an open debate was held by the past President of the BSSH for and against repair of digital nerves. The counter

argument against your comment “I consider a publication of this work with the resulting recommendation especially for young colleagues to be grossly negligent. The lack of care for peripheral nerve injury can harm those affected.” would be that many surgeons would find it grossly negligent for surgeons to continue the practice of a surgical intervention on patients without high quality evidence to justify the need to do so. To this effect the UK NIHR HTA has commissioned a call for a multi-centre randomised control trial to look at exactly this problem and provide high quality evidence to justify the continued practice by surgeons to undertake a digital nerve repair where currently no strong evidence exists to do so.

VERSION 2 – REVIEW

REVIEWER	J Lohmeyer Klinikum rechts der Isar, Technische Universität München, Germany
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	Return of normal sensibility is not uncommon, but the regular outcome in children. Hence the abstract should not give this misleading statement. The meaning of the following sentence is rather unclear: almost unrepaired nerves regained protective sensation by 6 months and all patients declined further surgery. The aim of the study is clearly stated: This systematic review aims to rigorously evaluate the evidence base for surgical repair of unilateral adult digital nerve laceration compared to no repair. The study aimed to determine differences in outcomes between surgical repair and no repair. Patient age and surgical experience level were found to be predicted factors for the outcome. The analysis still partly relies on rather old data, when microsurgery wasn’t broadly established. Those data should be neglected. I don’t see the point in undue bias. Microsurgical skills are essential. Sometimes some things are rather obvious. How could you repair properly, what you can barely see without magnification? Surgical skills are a regular positive predictive factor, it seems likely to believe magnification is one too. The following assumption is pure speculation and a personal opinion of the authors without proper references: “The neuroma incidence varied from 0-20% with a pooled incidence of 4.6% in the repaired group and 5% in the un-repaired group. For cold intolerance this varied from 2-53%. Therefore, there is no evidence that these complications are less likely following nerve repair compared to no repair.” This definitely has to be omitted. How can the authors possibly argue that this review has found only weak evidence to support the current practice of repairing all unilateral digital nerve injuries in adults. There was clearly too few

	data to compare with, as there is only few data on the necessity to repair or immobilize fractured bones (and no one whould argue). The main statement of the meta-analysis is based on a 1993 paper that compared 72 reconstructed nerves with 36 untreated ones. More recent findings are not included. However, it is confirmed that different factors exist that correlate with a better result. This also includes the experience of the surgeon. The statements derived from this are hardly valid for the low number of cases and the citation of a single 25-year-old study. The authors themselves emphasize that a better surgical experience goes hand in hand with a better return of sensitivity after the nerve suture. Thus, it also seems evident that the surgical care, if well performed, must have a positive effect. I continue to stress out that it is completely inadmissible to postulate such conclusions, especially since medical colleagues could be enticed to take the publication as a basis for no longer treating patients adequately. This has sever legal issues! As a reviewer, I do not want to be responsible for this and strongly advise against a publication!

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: J Lohmeyer

Institution and Country: Klinikum rechts der Isar, Technische Universität München, Germany

Please state any competing interests or state ‘None declared’: None declared

Return of normal sensibility is not uncommon, but the regular outcome in children. Hence the abstract should not give this misleading statement.

The title and abstract make it clear that this review and conclusions are drawn from the data on ADULT patients. We make no reference to the results in children.

The meaning of the following sentence is rather unclear: almost unrepaired nerves regained protective sensation by 6 months and all patients declined further surgery.

Thank you for pointing this out. We have added the word “all”.

The aim of the study is clearly stated: This systematic review aims to rigorously evaluate the evidence base for surgical repair of unilateral adult digital nerve laceration compared to no repair. The study aimed to determine differences in outcomes between surgical repair and no repair.

No response needed

Patient age and surgical experience level were found to be predicted factors for the outcome.

No response needed

The analysis still partly relies on rather old data, when microsurgery wasn’t broadly established. Those data should be neglected. I don’t see the point in undue bias. Microsurgical skills are essential. Sometimes some things are rather obvious. How could you repair properly, what you can barely see without magnification?

Surgical skills are a regular positive predictive factor, it seems likely to believe magnification is one too.

As per rigorous systematic review methodology we have included all data and commented and drawn conclusions appropriately. To omit data based on age of paper as reviewer 2 suggest would bias conclusions. As already stated in the paper and in our original response to the reviewers comments the pre-magnification papers did not document 2PD outcome and were therefore not included in the final analysis and therefore do not effect conclusions. Interestingly, contrary to reviewer 2's suggestion, there is also data to support the view that magnification makes no difference to surgical outcome (Marsh and Barton JBJS 1987).

The following assumption is pure speculation and a personal opinion of the authors without proper references:

"The neuroma incidence varied from 0-20% with a pooled incidence of 4.6% in the repaired group and 5% in the un-repaired group. For cold intolerance this varied from 2-53%. Therefore, there is no evidence that these complications are less likely following nerve repair compared to no repair."

This definitely has to be omitted.

We are unclear what reviewer 2 is trying to imply here and he is incorrect. These are not our opinion and not speculation. These are the documented and referenced papers that are presented. Table 4 even shows the individual detailed papers. This data is crucial and needs to remain.

How can the authors possibly argue that this review has found only weak evidence to support the current practice of repairing all unilateral digital nerve injuries in adults. There was clearly too few data to compare with, as there is only few data on the necessity to repair or immobilize fractured bones (and no one whould argue).

We have undertaken a methodologically sound and detailed review of the literature. We appreciate the results of the review are disturbing for reviewer 2 and he has strong personal opinions. As mentioned previously the NIHR have commissioned a multi-centre repair versus no repair digital nerve RCT based on the fact that there is weak evidence to support current practice. They have commissioned this call to provide the strong evidence to justify the continued practice of digital nerve repair. Reviewer 2's comparison to fracture fixation is not relevant, however, I am sure he is aware there is a trend now for more conservative non-operative fracture management and early mobilisation.

The main statement of the meta-analysis is based on a 1993 paper that compared 72 reconstructed nerves with 36 untreated ones. More recent findings are not included. However, it is confirmed that different factors exist that correlate with a better result. This also includes the experience of the surgeon.

The statements derived from this are hardly valid for the low number of cases and the citation of a single 25-year-old study.

This is not a meta-analysis and we have not claimed it to be. All data and papers have been included. There are no more recent findings. Irrespective of the 1993 paper the outcomes of nerve repair are poor with only 24% of patients overall regaining "normal" sensation. The outcome measure most commonly used is also known to be prone to a learning effect that leads to over inflated values. All the data we included and discussed was placed in the context of its poor quality, sample size, lack of comparators and often-historical nature.

The authors themselves emphasize that a better surgical experience goes hand in hand with a better return of sensitivity after the nerve suture. Thus, it also seems evident that the surgical care, if well performed, must have a positive effect.

No response required

I continue to stress out that it is completely inadmissible to postulate such conclusions, especially since medical colleagues could be enticed to take the publication as a basis for no longer treating patients adequately. This has sever legal issues!

It is disappointing that reviewer 2 holds such strong beliefs despite being presented with all the published data. Reviewer 2 fails to understand that surgeons are highly educated and sensible people who are able to comprehend data and make sensible conclusions themselves. For him to speculate that surgeons will stop repairing digital nerves based on this review are unfounded. It is actually incumbent upon surgeons during a discussion with the patient, as part of informed consent, to make them aware of the limitations of digital neurorrhaphy and to appropriately manage their expectations based on available evidence. This is our current legal obligation. The conclusions of our well conducted, methodologically sound review have highlighted the lack of high-quality evidence and supports further research into digital nerve repair, not lack of care as suggested.

As a reviewer, I do not want to be responsible for this and strongly advise against a publication!

We thank reviewer 2 for taking time to comment on our submission and we feel that his comments have helped us to refine and strengthen our paper. We are aware that his views on digital nerve repair represent those traditionally held by some surgeons and our hope is that he and others will have the courage to challenge their own beliefs in the face of this objective review of the evidence. Hopefully, he will be a staunch supporter of the digital nerve RCT as it will offer the opportunity once and for all to evaluate the benefits of digital nerve repair in adults.