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The use of CRP within a clinical prediction algorithm for the differentiation of septic arthritis and transient synovitis in children.

Singhal R, Perry DC, Khan FN, Cohen D, Stevenson HL, James LA, Sampath JS, Bruce CE
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Reviewers: Oliver Bradford and William Carlino

Introduction

We were interested to review this paper, as several children have recently presented to our department with an irritable hip. The paper by Kocher et al from 1999 in particular has provided a useful algorithm to date to aid clinical decision-making for this pathology, but the use of C-reactive protein (CRP) has superseded erythrocyte sedimentation rate (ESR) in most departments as a standard marker of acute inflammation. This study aimed to redefine the algorithm, including CRP as a variable.

Methods

This was a retrospective case-note review of a 5 year period of all children presenting with an acute atraumatic limp or hip pain to a UK tertiary level paediatric centre. An irritable hip protocol ensured ultrasound scan evaluation in all cases. Exclusion criteria were clearly stated, including neonates, no hip effusion on ultrasound, and confirmed differential diagnosis excluding transient synovitis or septic arthritis. A flow diagram presented the attrition rates of the study numbers. Of 735 children who underwent ultrasound scan, a yield of 311 demonstrated effusion of the hip (42%), with a mean age of 5.3 years, and a male to female ratio of 2:1.

Variables deemed significant included pyrexia of 38.5°C, inability to bear weight or move the leg in non-ambulant children, a white cell count (WCC) greater than 12.0x10⁹ cells/l and a CRP greater than 20mg/l. Final decision for arthrotomy and antibiotics versus observation was made by the lead clinician, accounting for clinical and haematological findings. No mention is made of the number of clinicians involved.

Results

Of the 311 children with confirmed effusion on ultrasound scan, 42 (13.5%) underwent arthrotomy. Of these, almost a third were negative (31%), while 69% proved positive for septic arthritis, 43% on joint aspirate culture, and 26% on synovial white count (++ or more white cells per high power field). The most common organisms were Staphylococcus Aureus (28%), followed by Streptococcus Pyogenes (22%), coagulase negative Staphylococcus (17%) and Streptococcus Agalactiae (11%). Including the negative

arthrotomies, the overall rate of transient synovitis was 91% (282) and septic arthritis 9% (29). In this study, 1 in 10 children with a positive hip effusion on ultrasound were diagnosed with proven septic arthritis.

Univariate analysis of explanatory variables (CRP, temperature, weight-bearing status and WCC) showed all four to be significant predictors ($p < 0.001$) of septic arthritis, with impressive odds ratios, in particular CRP (OR 81.9). Multivariate analysis to evaluate the independent significance of individual variables excluded temperature and WCC from further analysis due to loss of independent significance. CRP and weight-bearing status remained significant, and a final two-variable probability algorithm demonstrated a probability of $< 1\%$ of septic arthritis in patients able to bear weight with a CRP $< 20\text{mg/l}$, and 74% in patients unable to bear weight with a CRP $> 20\text{mg/l}$.

Children with no effusion demonstrated on ultrasound scan were followed up to 3 months, with complete spontaneous recovery reported in all. Within the limits of this short follow-up period, albeit for an acute disease process, this gives a sensitivity of ultrasound of 100% in excluding septic arthritis of the hip if no effusion found, and a specificity of 57% for septic arthritis of the hip if an effusion was present. Ultrasound therefore is useful in ruling out septic arthritis, with no false negatives in this study. Positive predictive value was 9%, with a negative predictive value of 100%.

Discussion

Strengths

- The study question is relevant. Substitution of CRP in the place of ESR aligns with contemporary clinical practice. Previous algorithms have included CRP alongside ESR, but this study provides justification for the use of CRP as a more widely used, cheaper, reproducible and direct measure of the acute phase reaction to inflammation.
- The study is from the UK, and although conducted on a tertiary level paediatric centre population, is generalisable to children presenting across the Kingdom. All variables measured and investigations used are already in common use across the UK; therefore the results can be directly applied to current practice of the readership.
- The relevance of differential diagnoses identified (discitis, aneurysmal bone cyst, juvenile rheumatoid arthritis, Perthes' disease, lower limb fracture, neurological or rheumatological disease and non-hip-related infection), benefit of ultrasound, significance of variables studied, and common organisms identified have clinical application relevant to Paediatric, Rheumatology and Orthopaedic clinicians.
- Study criteria, including exclusions and attrition rates were clearly illustrated
- Statistical analysis employed was comparable to previous studies, allowing direct comparison of data and results. The data itself was subject to appropriate and rigorous analysis, which is expanded upon in the results section.
- Use of ultrasound in an 'irritable hip protocol' was demonstrated as an investigation to rule out septic arthritis, with 100% sensitivity.

Limitations

- The study design is retrospective, with no power calculation performed

- The values designated for the 'significant findings' for temperature, CRP and WCC used to define them as binary variables were referenced from the landmark paper by Kocher et al (1999). No justification is given in either paper as to why these specific values were chosen as significant (CRP > 20mg/l; temperature > 38.5°C; WCC > 12.0x10⁹ cells/l). An analysis of these variables as continuous data might have yielded more information, and a revised value for 'significance' to produce an algorithm with higher probabilities with positive variables (e.g. CRP > 30mg/l).
- The use of '++' white cells in synovial fluid to confirm septic arthritis was questionable. Many joint aspirates come back as 'numerous/++ white cells, with no organisms seen' and often a conservative approach of close clinical monitoring is adopted. Further clarification of the number of white cell numbers required to confirm septic arthritis, in the absence of organisms, is required.
- No reason is documented for the exclusion of joint aspiration as part of their work-up for a child with an irritable hip. We consider, where it is felt indicated, that aspiration of frank pus versus clear synovial fluid from the hip joint would be helpful in clinical decision-making to proceed to arthrotomy and washout of joint.
- No consideration is given in the discussion to the role of MRI. A useful list of differential diagnoses was included. If no effusion is present in a child refusing to bear weight and with raised inflammatory markers, MRI can be used to rule out other pathologies approximate to the hip joint, and guide further management. In our unit, we consider selective use of both joint aspiration and MRI part of our work-up in children presenting with an irritable hip.
- No comment is offered regarding the number and experience of the technicians performing the ultrasounds scans. Ultrasound does however have a high sensitivity for detection of effusion of the hip in published literature.
- No comment is offered regarding the number of clinicians making the final decision to progress to arthrotomy
- No data is presented regarding post-operative complications from arthrotomy. Although arthrotomy is not the primary focus of this study, inclusion of complication data for completeness would be useful when counselling patients and parents

Conclusion

This paper provides a valuable reference for clinicians faced with a child presenting with an irritable hip. Updating the original work by Kocher et al (1999) has shown the use of CRP in prediction of septic arthritis, particularly in helping rule it out, which justifies its current usage as the standard marker of acute inflammation, superseding ESR. The algorithm is widely applicable to units around the UK, using variables that are already in use, and ultrasound, which is readily available, dynamic, sensitive and safe. Consideration must still be given to the experience of the ultrasound technician, not quantified in this paper, and the final decision to proceed to arthrotomy must still be based on clinical experience. We would propose selective use of joint aspiration and MRI to further aid diagnosis and management. As with all algorithms, they are not absolute, but provide a useful adjunct to both guide and justify decision-making in often complex pathologies.

The non-operative functional management of patients with rupture of the Tendo Achillis leads to low rates of re-rupture

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Reviewers: Tom Mendes da Costa and Lawrence Moulton

Introduction

The choice of operative or conservative treatment for acute rupture of the Tendo Achillis (TA) is a common discussion between patients and the on-call Orthopaedic team, with functional demand, re-rupture rates and operative complications the main criteria for basing the decision. Many would advocate operative intervention for young, high demand patients to preserve maximal function and minimise re-rupture rates, opting for conservative management in older patients or those with co-morbidities where loss of function may be less apparent or outweighed by the risk of wound complications. Treatment for all patients along this spectrum remains controversial.

Acknowledge this controversy, the authors present a single centre, single surgeon retrospective review of 945 patients (949 tendon ruptures). The authors report no difference in re-rupture rates and excellent functional recovery using non-operative management across all age groups, co-morbidities and functional requirements.

Methods

A retrospective review of a single centre, single surgeon series of 975 patients diagnosed with TA rupture in Northern Ireland over a twelve year period (1996-2008). The decision to treat conservatively was based on clinical grounds alone using approximation of tendon ends on palpation for all acute presentations (<2 weeks) and 71 delayed presentations. Ultrasound assessment was used in equivocal cases resulting in 26 delayed cases where tendon ends did not oppose undergoing operative fixation and excluded from further study. One patient too obese for a pneumatic walker (the standard conservative treatment orthosis) was treated in casts and excluded. Additionally three patients had been operated upon prior to referral and were excluded also.

All patients treated non-operatively followed the same functional management protocol, although the orthosis was changed part way through the study. This involved four weeks immobilisation in a non-weight-bearing equinus cast followed by a pneumatic walker with heel raises that are reduced every 2 weeks. At 8 weeks the walker is removed and the patient commences physiotherapy and is finally seen at 14 weeks and discharged once a specialist physiotherapist deems the ankle strength satisfactory. The degree of weight bearing permitted in the pneumatic walker is not specified but early mobilisation is assumed.

Outcome measures regarding return to work, sporting activity, satisfaction with treatment and complications such as stiffness and weakness were obtained from a questionnaire completed by the patient, with major complications such as DVT, PE and re-rupture obtained from medical notes. Patients were discharged when an objective measurement of strength was deemed satisfactory by a specialist physiotherapist, when the patient was satisfied, or after three DNA episodes. Paired t-test was used to analyse the data.

Results

Overall re-rupture rate was 2.8% (27 ruptures), all within 3 months of diagnosis. There was no significant difference between re-rupture rates based on patients sporting activity, sex or time of presentation.

99.4% of patients had good to excellent subjective scores on discharge, although assessment details are not reported. Six patients (<1%) needed operative intervention due to tendon lengthening leading to weak dorsiflexion.

Orthosis-related complications were low, all resolving on cessation of immobilisation. Major complications such as DVT and PE and foot drop were all < 0.2%

Discussion**Strengths**

- Single centre, single surgeon trial with homogenised management protocol (except the change in orthosis)
- Data collection not performed by treating surgeon
- Large study with long follow-up
- Low loss to follow-up.
- Appropriate statistical tests
- No conflicts of interest
- Poses and answers a discreet question of clinical relevance

Weaknesses

- The protocol is not clearly defined (i.e. how much plantar flexion, how much is this decreased, what is the weight bearing status etc), which makes it very difficult to reproduce this in other settings.
- Patient recall bias (timing of questionnaire unclear)
- < 1% loss to follow up is reported, which for a study of this size and length is very low
- Possibility of missing late rupture in some (follow up 2-12 years)
- No explanation of formal scoring for functional outcome. (Reference is made to a paper previously published by the same unit in JBJS American, however this is only a subset of the patients)
- Evidence for 14 days as cut off for delayed presentation
- No analysis of results for age / co-morbidities (are all re-ruptures in over 50s)
- No comparison group e.g. compare complication rates and functional outcomes to other studies, not just re-rupture rates.
- Clinical assessment of rupture –is this reproducible and accurate.
- Change of prosthesis after 180 cases

- Was the protocol adjusted for bilateral ruptures (as unable to PWB)

Conclusion

The authors conclude that strict adherence to their non-operative treatment protocol results in re-rupture rates similar to that of operative intervention dispelling using concerns regarding re-rupture to justify operative fixation. The reduction in re-rupture rate utilising operative fixation shown by the 2010 Cochrane meta-analysis is challenged due to the high prevalence of casting, as opposed to a functional orthosis and early mobilisation used in the authors' series. The authors advocate non-operative functional management in patients of all ages, co-morbidities, levels of function, and even for delayed presentations if tendon apposition is possible, proposing low complication rates and a return to pre-injury sporting levels.

Reducing the number of TA operative repairs would be financially beneficial to hospital trusts and avoid the potentially devastating complication of wound breakdown. The authors have provided compelling evidence that re-rupture rates may be comparable to operative treatment but further analysis on functional outcome, imperative to a population with ever-increasing functional demand, is needed across all age groups before non-operative functional management can be universally advocated.

Total hip replacement and hemiarthroplasty in mobile, independent patients with a displaced intracapsular fracture of the femoral neck: a seven- to ten-year follow-up report of a prospective randomised controlled trial

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Reviewers: A Hanoun and N Furness

Introduction

This was a medium term follow-up report of the 7- to 10 year results of a previously reported prospective randomised controlled trial published by the same authors in 2006. The study compared total hip replacement (THR) with hemiarthroplasty for the treatment of mobile independent patients who suffer a displaced intracapsular fracture of the neck of femur. The original results were that THR in this injury produced better functional outcome than hemiarthroplasty after three years with better Oxford hip scores and longer walking distances. The main aim of this follow-up study was to see whether the difference still exists after a prolonged period.

Methods

The study was designed to isolate the bearing surface of the acetabulum as the sole variable. To achieve this, the authors standardised the femoral component (in this case the cemented CPT) and the approach (trans-gluteal) used to implant the device. There was no significant difference in the grade of surgeon operating on the two patient groups. In those patients selected for hemiarthroplasty the Endo Femoral Head in 2mm increments was used and in the THR group a 28mm metal-on-polythene, cemented acetabular cup used.

Inclusion criteria

- Age >60 years old.
- Independent living status.
- Able to walk half a mile prior to injury.
- Non-pathological fracture.
- No or minimal osteoarthritis on X-ray.
- Normal abbreviated Mini Mental Test score.

Randomisation method

- Sealed envelope.

Outcome measures

- Current Oxford Hip Score.
- Short-Form 36 (SF-36).
- Self reported walking distances.
- Antero-posterior and lateral radiographs of the hips were assessed for
 - femoral and acetabular osteolysis.
 - linear polythene wear of the acetabular component.

Statistical analysis

- Mann-Whitney U test was used to compare the OHS and SF-36 scores.
- Walking distance was compared using the Student's t-test (after logarithmic transformation).
- Wilcoxon-rank test to compare old and new OHS.
- Analysis of Variance (ANOVA) used to compare old and new walking distances (again following logarithmic transformation).
- Z-scores used to analyse mortality rates.
- Fisher's exact test to compare revision rates.
- Kaplan-Meier analysis (95% CI) compared survival using Breslow test for significance.
- Level of significance set at a p-value of <0.05.

Results

The original study recruited 81 patients with a mean age of 75 at enrolment from two study centres who were randomised into two groups, 40 patients undergoing THR and 41 hemiarthroplasty. No significant differences between the patient populations were found.

Of the 40 patients who underwent a THR, 27 were still alive at follow-up. Incomplete data was obtained from six patients for a variety of reasons, leaving 21 with a full data set.

Of the 41 patients who underwent hemiarthroplasty, 20 were still alive at follow-up. Incomplete data was obtained from seven patients leaving 13 with a full data set.

- Mean follow-up was nine years (7-10).
- Overall mortality was 32.5% and 51.2% for THR and hemiarthroplasty respectively (this difference was not statistically significant ($p = 0.09$)).
- At 100 months a significantly larger number of hemiarthroplasty patients had died. ($p = 0.026$).
- Significant increase in survival after THR ($p = 0.013$).
- Dislocation rate: 3 in THR group versus none in hemi group.
- Actual revision rate: 1 in THR group versus 4 in hemi group.

(Although the authors did mention that revision was indicated in significantly more of the hemiarthroplasty group: 8 vs. 1 ($p = 0.015$))

- The average walking distance:
 - 0.72 miles for THR group
 - 0.59 mile for hemiarthroplasty group(Note this was not statistically significant ($p = 0.487$))
- The average Oxford Hip Score:
 - 23.1 for the THR group
 - 22.5 for the hemiarthroplasty group(No p value was given)
- The average SF-36 physical score:
 - 37 for the THR group
 - 31.1 for the hemiarthroplasty.(Note this was not statistically significant ($p = 0.152$))
- The average SF-36 mental score:
 - 54.4 for the THR group

- 53.6 for the hemiarthroplasty.

(No p value was mentioned)

Conclusion

The study concluded that THR confers a significant advantage over hemiarthroplasty in terms of mortality in this patient group. There was a trend towards a better functional outcome in THR patients; however the significant difference seen earlier on in this study was not born out in the medium term.

Strengths

- Relevant topic especially given changes in NICE guidelines.
- Randomised, controlled trial conducted over more than one site.
- Well controlled variables – effective isolation of acetabular bearing surface.
- Similar demographics between both patient groups.
- Standardised stem – The use of an identical femoral component ruled out implant bias.
- Low loss to follow up - 4% loss in this patient group is low. They made the most of a small final sample size.
- Validated outcome measures - OHS and SF-36 have been independently validated and widely used.
- Use of appropriate statistical methodology.
- Plain English – The study was well written and read easily.
- No financial / commercial backing.

Limitations

- Small sample size due to patient death leading to low statistical power.
- A significantly higher proportion of hemiarthroplasty patients died compared to THR, which may indicate an inferior general health that was not detected at the time of the original surgery. It is possible that this difference in mortality is a result of the hemiarthroplasty, but this was not mentioned or explored in the paper.
- Confusion regarding difference in survival statistics at the end of the study between the two groups. Is p – value 0.026 or 0.013? And how was the later calculated?
- Incomplete radiographical analysis - 18 THR versus 8 in the hemi group.
- Study used hemiarthroplasty sizes in 2mm increments when 1mm is the norm – this could lead to size mismatch and may explain higher rate of erosion and pain in the hemi group.

Review summary

This is a well-designed study aimed at answering a common question. It is one of very few randomized controlled trials undertaken in this subject and the only one where the only variable is the acetabular bearing surface. Despite the loss in follow up due to mortality, the conclusion that THR is superior in the

short term is justified for the time being, despite the loss of the difference in the medium term. This conclusion reinforces NICE guidelines stating that THR should be considered in this group of patients. It also demonstrates the difficulty of conducting trials in this group of patients; however, a similar study with higher patient numbers is still needed for definitive answer.

Tranexamic acid in total knee replacements: A systematic review and meta-analysis.

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Reviewers: Alex Riddell and Josephine McEwan

Introduction

Total knee replacements are frequently associated with substantial blood loss necessitating allogenic blood transfusion, which may lead to complications such as haemolysis, acute lung injury and even death. A number of technologies to reduce the need for transfusion are available but their role thus far has been controversial and most are not routinely used. This paper is a systematic review and meta-analysis of randomised control trials (RCT) evaluating the effect of tranexamic acid (TXA) on blood loss and transfusion in primary total knee replacement. It also evaluates the changes in adverse clinical outcome such as re-operation and complications including DVT, PE, infection, ischaemic heart disease and mortality. This paper follows a similar paper by the same group into the use of tranexamic acid in total hip replacements which was published in the JBJS [Br] in January 2011.

Methods

Aims

To consolidate the trials so far and thereby evaluate the effect of TXA on blood loss and transfusion as well as on adverse clinical outcomes.

Ethics

No ethical considerations are stated.

Study type/Level of evidence

Systematic review and meta-analysis of RCTs. Each RCT was assessed and given a total quality assessment score (QAS) to create an overview; however, this score was not used to weight the studies in the meta-analysis. Multiple RCTs were included but note is made of the significant heterogeneity between the studies and hence this paper would be classed as level 1a- based on centre for evidence based medicine, Oxford, UK.

Material

The review used a generic tool for evaluation as designed by the Cochrane Bone, Joint and Muscle Trauma Group. RCTs of adult patients undergoing primary knee replacement of any type were identified for evaluation. Synchronous or sequential bilateral primary TKR and revision TKR were excluded. The use of TXA was considered the intervention and placebo or no treatment was considered as the control. Papers between 1966 and December 2007 were identified via an extensive online search and were selected for inclusion based on two separate authors' opinions with senior authors ruling over any disputes.

Outcome**measures**

The primary outcome measure was the proportion of patients who underwent autologous blood transfusion, allogenic blood transfusion or both. The secondary measures were number of units transfused, length of hospital stay, volume of peri-operative blood loss, functional knee outcome measures, quality of life outcome measures and complications (death, myocardial infarction, stroke, DVT, PE, DVT, renal failure and re-operation due to bleeding).

Statistics

Review Manager (RevMan 5, The Nordic Cochrane Centre, Copenhagen, Denmark), was used to express the findings and combine the estimates of the effects of treatment. Forest plots provide a summary of overall effect of treatment. The Mantel-Haenszel method was used to combine studies using a fixed effects model. Subgroup analyses were attempted but three out of five of these analyses were impossible to complete due to lack of data. Intention-to-treat principles were used when data was unavailable from authors or through loss to follow-up.

Results

The search revealed 323 potential studies of which 297 were excluded and 19 placebo controlled RCTs were included. Most trials were small and included between 24 to 136 participants but were well designed and scored highly on the quality assessment score.

Different doses and modes of delivery of TXA were noted. Doses ranged from 700 mg to 10,500 mg. TXA was administered intravenously (n=17), orally (n=1) and topically (n=1).

Low molecular weight heparin thromboprophylaxis was used in the majority of studies (n=17), although aspirin was used in one study and no chemical thromboprophylaxis was used in another.

- Blood transfusion (14 studies with 824 participants) – A variety of transfusion triggers were used by the different trials and these are included in the paper. Overall TXA led to a reduction in proportion of patients requiring blood transfusion (RR 2.56; 95% CI 2.10 to 3.11; $p < 0.001$). Trials consistently suggested benefit but significant heterogeneity was noted ($Q p < 0.001$; $I^2 = 75\%$).
- Amount of blood transfusion (13 studies with 791 participants) – Crude pooled data indicated a fourfold rise in the number of units transfused when TXA is not used.
- Blood loss – Post-operative (drain) and total blood loss measurements were reviewed separately. TXA reduced post-operative blood loss by a mean volume of 245 ml (95% CI 213 to 278; $p < 0.001$. $Q p < 0.001$; $I^2 = 89\%$). TXA reduced total blood loss by a mean volume of 591ml (95% CI 536 to 647; $p < 0.001$. $Q p < 0.001$; $I^2 = 78\%$)
- Length of stay (2 studies with 60 participants) – Mean reduction 0.76 days, $p=0.17$
- DVT (13 trials with 801 participants) – No increase in DVT in TXA group, $p=0.98$.
- PE (19 trials with 971 participants) – 4 patients had PE in control group and 1 in TXA group, $p=0.5$
- Mortality – 2 deaths in total, 1 from PE in control group and 1 in TXA group 6 months post operatively with unrelated cause of death (not stated).
- Subset analysis of TXA dose and blood transfusion rate showed larger clinical benefit of TXA in doses $>4000\text{mg}$, $p<0.001$.

Discussion**Strengths**

- The paper has consolidated and summarised the data of TXA on blood loss post-TKR and suggests some significant results
- Extensive search methods to identify all relevant papers
- Effort made to obtain missing data, not just imputations
- High QAS for trials included
- Shows statistically significant benefit of IV TXA in larger dose on reducing bloods loss and need for transfusion
- Discusses other published meta-analyses and their strengths/weaknesses

Limitations

- Publication bias: smaller trials with negative findings unlikely to be published
- Many other TKR RCTs of TXA have been published in the past 2-3 years which have not been included
- Significant heterogeneity, therefore unable to fully assess the full impact of the significant findings. Variations include dosage/route of TXA, timing of administration of TXA, surgical technique, trigger for transfusion
- Used a fixed effects model when applying the Mantel-Haenszel method when a random effects model should probably have been used in view of the significant heterogeneity
- Lacked power in subset analyses
- 297 trials excluded but limited information given with regards the way the studies were selected
- State findings of some excluded trials to corroborate findings of included trials
- Not all the outcome measures eg stroke, MI have been commented on
- Insufficient data to perform functional outcome assessments

Conclusions

The authors acknowledge that there is controversy surrounding the use of anti-fibrinolytics. They also admit that the level of heterogeneity undermines the significance of some of their findings. Importantly, they do state that although theoretically TXA has a risk of thrombosis, this has not yet been clinically proven. Their analysis of DVT/PE risk in participants of the trials only included a maximum of 971 patients and to find an increase in risk of 1% would require 5,000 participants.

The meta-analysis has demonstrated that IV TXA reduced blood loss and need for transfusion but has not demonstrated whether or not this has any impact on clinical outcome or morbidity, nor has it conclusively proven that administration of TXA is not associated with harm. Further work is therefore needed.