Systematic Review Protocol

Title/Topic:
Benefits and associated risks of using allograft, autograft and synthetic bone fusion material for patients and service providers – A Systematic Review

Centre conducting review: Edinburgh Napier University

*Primary reviewer:* Gillian Altken
Reviewer affiliated to Joanna Briggs Institute
Collaborating Centre, Robert Gordon University, Aberdeen, UK

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Reviewer affiliated to Joanna Briggs Institute
Collaborating Centre, Robert Gordon University, Aberdeen, UK

*Commencement date:* June 2010

*Expected Completion date:* December 2010
Review Questions/Objectives

The review objective is to determine the benefits and associated risks of using autograft, allograft and synthetic bone fusion material for patients and service providers relating to spinal fusion.

The review questions are:

- What are the benefits to patients relating to the use of autograft, allograft or synthetic bone fusion material when undergoing spinal fusion?
- What are the associated risks to patients relating to the use of autograft, allograft or synthetic bone fusion material when undergoing spinal fusion?
- What are the benefits to service providers relating to the use of autograft, allograft or synthetic bone fusion material when undergoing spinal fusion?
- What are the associated risks to service providers relating to the use of autograft, allograft or synthetic bone fusion material when undergoing spinal fusion?

Background

Spinal fusion is a surgical procedure used to correct problems with the vertebrae such as protrusion and/or degeneration of the cushioning disk between vertebrae (sometimes called slipped disc or herniated disc), abnormal curvatures of the spine (such as scoliosis or kyphosis), weak or unstable spine caused by infections or tumours, injuries to the spinal vertebrae. Each of these can cause pain, reduced mobility and cause other associated problems amongst people who suffer from these conditions and spinal fusion is seen as a procedure that can improve and/or prevent worsening of these symptoms. The documented number of spinal fusions within the US per year is 200,000 and is increasing\textsuperscript{1,2}. The cost per procedure is estimated to be $34,000 excluding professional fees.

In spinal fusion a solid bridge is formed between two, or more, vertebrae to prevent movement between them. Bone graft or bone graft substitute (BGS) is used to enable a solid bridge to form. In many cases the spine is initially stabilized by using metal rods and/or screws however in the long term fusion is an achieved using bone graft. Fusion does not occur at the time of surgery; rather the bone graft enables the development of fusion over time with the gradual growth of new bone so providing integrity and consequent stability\textsuperscript{2}. For the purposes of this review we will focus only on bone grafts and BGS procedures which are used to repair skeletal defects, enable fusion and fill voids in the bone. It will explore the benefits and associated risks of these procedures for patients to contribute to the evidence underpinning these procedures.

Bone is one of the most commonly used materials to help promote fusion of the vertebrae at the moment. This bone can come from another site from the recipients own body (autograft) or from a donor (allograft); additionally several synthetic bone fusion materials (BGS) are available, based on a variety of materials such as ceramics and polymers and may be formulated with biological material to theoretically increase their efficacy. Currently the choice of material used is dependent on a number of factors, the type of spinal fusion required, and local training programmes. There is a lack of evidence based guidance in this area\textsuperscript{3}. 
The use of autograft bone involves the individuals own bone being harvested (usually from the iliac crest) which although requiring two surgical procedures has been considered the ‘gold standard’ for spinal fusions as it has the necessary characteristics to allow the growth of new bone and subsequent fusion of vertebrae\(^4\). The bone provides a calcium scaffold required to support the new bone growth and provides osteoblasts and bone morphogenetic proteins (BMP) required for new bone growth. The procedure has the perceived advantages for patients of no risk of disease transmission, little risk of rejection and the potential for the growth of new bone tissue. However the morbidity associated with this procedure e.g. pain, infection and numbness are commonly reported\(^5,6\). Despite the common use of autologous bone there is little direct clinical evidence in support of its use\(^7\). Other factors such as the patients’ general health and for example whether or not they are a smoker will have a major effect on the successfulness of the procedure; in addition to the availability of a suitable bone supply.

Allograft bone can be donated from another patient (i.e. during a procedure such as a primary hip replacement) or from a cadaver and the major advantage of using allograft for spinal fusion is that it removes the need for an additional surgical procedure so eliminating donor site problems such as infection\(^8\). Allografts are osteoconductive, providing a scaffold for new repair however do not produce osteogenic cells and therefore are said to be more slowly incorporated into the existing vertebrae than autografts\(^3\). Some studies have found allograft to be as successful as autograft in producing successful fusion\(^8,9\) but the associated risks of allograft such as the potential for immunological reaction, transmission of disease\(^10\) need to be considered with the fact that the effectiveness of the allograft will also be affected by the health of the donor, the type of allograft used, the anatomical site of fusion and the patients age\(^11\). The fusion rate has been found to be similar between autograft and allograft in single level fusion but less effective in allograft when multiple fusions are undertaken\(^12\).

Allogenic bone tissue can be acidified to produce demineralised bone matrix (DBM) which will retain the osteoinductive growth factors and reduce this risk of disease transmission. However the quality and consistency of DBM is variable due to the inconsistent quantity of BMP that can be detected within it. As each donor is different and the sterilisation and processing techniques vary widely the physical and biological characteristics of the material can markedly change between batches and at times the level of BMP has been detected to be lower than therapeutically useful\(^11\).

For a number of reasons, including the risk associated with allograft and autograft and the more recent focus on the governance concerning its use, the use of synthetic bone graft material is becoming more prevalent within the healthcare arena. There are several formulations of synthetic products available these include BMP and synthetic bone grafts. Synthetic bone grafts include calcium phosphates and other ceramics. These materials are often used in combination with bone to facilitate fusion.

Synthetic material has the advantage of being sterile and therefore free from human pathogens and is available in unlimited quantities and in different shapes and sizes. Additionally no surgical procedure is required to obtain it. It is because of these qualities and the recent focus on the governance surrounding tissue from cadavers and consent for recipients of human tissue that a number of studies have been undertaken to compare these products with allograft and autograft material. Garrison et al\(^13\) identified BMP to be more effective than autogenous bone graft based on results obtained from radiographic fusion (as opposed to a CT scan) in individuals with single level degenerative disc disease and identified a reduction in both operating time and length of hospital stay. However they did not show any significant improvements on quality of life or economic data.
It is currently unclear which material is the most efficacious in the treatment of spinal fusion with the literature providing conflicting and variable information. A Cochrane review of fresh or frozen bone in hip arthroplasty found no suitable studies for inclusion and as a result recommend well designed randomised control trials to directly compare fresh and frozen allograft. Samartzis et al. are currently undertaking a Cochrane review of post operative pain management in spinal surgery patients, while this information will add to our review it concentrates specifically on pain management while we wish to look at other aspects associated with spinal fusion such as quality of life and functional ability.

The aim of this review is to explore research findings in relation to spinal fusion where either human tissue or a synthetic alternative are used and to determine the potential benefits and associated risks both to patients and service providers. In particular to explore the in depth effects on individuals undergoing spinal fusion surgery including length of both operative time and hospital stay, treatment satisfaction, quality of life, functional ability and post-operative pain and whether these are altered by the type of fusion material used. This area is currently overlooked in the majority of studies published in this area which concentrate on clinical efficacy. We aim to use an explicit and exhaustive search strategy with rigorous methodological analysis to synthesise the currently available information in this area to aid clinical decision making in spinal fusion.

Inclusion Criteria

Types of participants
The review will consider studies that include adult (16 and over) patients who have undergone a spinal fusion procedure, for any reason, using autograft, allograft or synthetic bone fusion material and service providers for spinal fusion procedure.

Types of interventions
Spinal fusion procedure, for any reason, using autograft, allograft or synthetic bone fusion material for adult (16 and over) patients.

Types of outcomes
Benefits to patients, benefits to service providers, associated risks to patients, associated risks to service providers, such as but not limited to (measured using all the methods, instruments, scales used/specified by authors of primary research studies):

- Length of hospitalisation post operatively
- Postoperative pain
- Patient mobility
- Post operative infection
- Quality of Life / Functional ability
- Treatment satisfaction.

Types of studies
This review will consider any quantitative experimental studies including RCT, cluster controlled trails, cross-over studies. In the absence of experimental trials we'll consider any quantitative non-experimental studies that address the objectives of the study.
Search strategy
A comprehensive search strategy will be developed to find both published and unpublished studies in English from 1989-2009. Due to the recent nature of developments in this area, only papers published in English within the last 20 years will be considered.

A three step search strategy will be used. An initial limited search of CINAHL, EMBASE and MEDLINE will be undertaken to identify key words. A second search will then be undertaken using all identified key words. The third stage will be to search the reference lists of all identified reports and articles for additional studies to ensure all relevant material is captured. MeSH terms and keywords will be adapted to suit the individual databases.

The databases to be searched include: MEDLINE, CINAHL, Embase, DARE, PubMed. Cochrane Library, JBI, Clinical Evidence.

The search for unpublished studies will include: Proceedings; dissertations; abstracts; reports.

Initial keywords to be used will be: spinal fusion, bone transplantation, bone substitute.

Medline
Spinal Fusion

Search Strategy

1. exp spinal fusion/
2. (spin$ adj2 fus$).ti,ab.
3. exp bone transplantation/
4. (bone adj2 fus$).ti,ab.
5. exp bone substitute/
7. or/1-6
8. exp quality of life/
9. exp pain, postoperative/
10. 7 and 8
11. limit 11 to (english language and humans and yr="1990 -Current" and "all adult (19 plus years")")
12. 7 and 9
13. limit 13 to (english language and humans and yr="1990 -Current" and "all adult (19 plus years")")
14. 7 and 10
15. limit 15 to (english language and humans and yr="1990 -Current" and "all adult (19 plus years")")
Embase
Spinal Fusion

Search Strategy

1. exp spinal fusion/
2. (spin$ adj2 fus$).ti,ab.
3. exp bone transplantation/
4. (bone adj2 fus$).ti,ab.
5. exp bone substitute/
7. or/1-6
8. exp quality of life/
9. exp pain, postoperative/
10. 7 and 8
11. limit 11 to (human and english language and yr="1992 -Current" and (adult <18 to 64 years> or aged <65+ years>))
12. 7 and 9
13. limit 13 to (human and english language and yr="1992 -Current" and (adult <18 to 64 years> or aged <65+ years>))
14. 7 and 10
15. limit 15 to (human and english language and yr="1992 -Current" and (adult <18 to 64 years> or aged <65+ years>))

CINAHL
Spinal Fusion
Search Strategy

1 (MH "Spinal Fusion")
2 TI spin* N2 fus* or AB spin* N2 fus*
3 (MH "Bone Transplantation")
4 TI bone N2 fus* or AB bone N2 fus*
5 (MH "Bone Substitutes")
6 TI bone N2 substit* or AB bone N2 substit*
7 S1 or S2 or S3 or S4 or S5 or S6
8 (MH "Quality of Life+")
9 (MH "Postoperative Pain"
10 S7 and S8 Limiters - Publication Year from: 1990-2010; English Language; Age Groups: All Adult
11 S7 and S9 Limiters - Publication Year from: 1990-2010; English Language; Age Groups: All Adult
Assessment of the methodological quality
Quantitative research papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the JBI -MAStARI (Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion with a third reviewer.

Data extraction:
Data from quantitative research studies will be extracted using the standardised Data Extraction Tool from the JBI-MAStARI (Meta Analysis Statistics Assessment and Review Instrument) (Appendix II).

Data synthesis
Where meta-analysis is possible quantitative research findings will be pooled in statistical meta-analysis using JBI-MAStARI software. All results will be double entered. Odds ratio (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed using the standard Chi – square test. Where statistical pooling not possible the finding will be presented in narrative form.

Acknowledgements
None

Potential conflicts of interest
None

References:
Appendices

Appendix I

JBI Critical Appraisal Checklist for Experimental Studies

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<th>Question</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<tr>
<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions?</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include [ ] Exclude [ ] Seek further info. [ ]

Comments (Including reasons for exclusion)

_________________________________________________________________
_________________________________________________________________
_________________________________________________________________
1. Is sample representative of patients in the population as a whole?  
2. Are the patients at a similar point in the course of their condition/illness?  
3. Has bias been minimised in relation to selection of cases and of controls?  
4. Are confounding factors identified and strategies to deal with them stated?  
5. Are outcomes assessed using objective criteria?  
6. Was follow up carried out over a sufficient time period?  
7. Were the outcomes of people who withdrew described and included in the analysis?  
8. Were outcomes measured in a reliable way?  
9. Was appropriate statistical analysis used?  

Overall appraisal:  Include □  Exclude □  Seek further info □

Comments (including reason for exclusion):
# JBI Critical Appraisal Checklist for Descriptive/ Case Series

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<tr>
<td>1. Was study based on a random or pseudo-random sample?</td>
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<td>2. Were the criteria for inclusion in the sample clearly defined?</td>
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<td>3. Were confounding factors identified and strategies to deal with them stated?</td>
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<td>4. Were outcomes assessed using objective criteria?</td>
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<td>5. If comparisons are being made, was there sufficient descriptions of the groups?</td>
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<td>6. Was follow up carried out over a sufficient time period?</td>
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<td>7. Were the outcomes of people who withdrew described and included in the analysis?</td>
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**Overall appraisal:** Include [ ] Exclude [ ] Seek further info [ ]

**Comments (Including reason for exclusion):**
Appendix II

JBI Data Extraction Form for Experimental/Observational Studies

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Clinical outcome measures

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**Continuous data**

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**Authors Conclusions**

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**Comments**

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