New Interventions for Lumbar Disc Herniation

Rickers, Kresten Wendell

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

NEW INTERVENTIONS FOR LUMBAR DISC HERNIATION

BY
KRESTEN WENDELL RICKERS

DISSERTATION SUBMITTED 2021

AALBORG UNIVERSITY
DENMARK

NEW INTERVENTIONS FOR LUMBAR DISC HERNIATION

by

Kresten Wendell Rickers

AALBORG UNIVERSITY
DENMARK

Dissertation submitted 2021

.

Dissertation submitted: 20 April 2021

PhD supervisor: Associate Prof. Søren Eiskjær MD
Aalborg University Hospital, Denmark

Assistant PhD supervisors: Associate Prof. Peter Heide Pedersen MD, PhD
Aalborg University Hospital, Denmark

Michael Bendtsen MD, PhD,
Aarhus University Hospital, Denmark

PhD committee: Associate Professor Thomas Jakobsen
Aalborg University

Peter Helmig, Consultant, PhD
Aarhus University Hospital

Professor Ilkka Juhani Helenius
University of Helsinki and Helsinki University Hospital

PhD Series: Faculty of Medicine, Aalborg University

Department: Department of Clinical Medicine

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-938-1

Published by:
Aalborg University Press
Kroghstræde 3
DK – 9220 Aalborg Ø
Phone: +45 99407140
aauf@forlag.aau.dk
forlag.aau.dk

Printed in Denmark by Rosendahls, 2021

PREFACE

Working on this PhD has been a long and exciting process at times very challenging. The project started in Aarhus with the development of a method for repairing the annulus fibrosus. The Orthopedic Surgery Research Laboratory conducted research into cartilage regeneration, and the intention was to use a method based on results from there. In a broad collaboration with, among others, the Interdisciplinary Nanoscience Center at Aarhus University and the Vrije Universiteit in Amsterdam, a bio scaffold was developed and tested. This facilitated a very interesting and rewarding stay at the research group at the Research Institute MOVE in Amsterdam where the method was tested in their biomechanical laboratory.

Unfortunately, the scaffold did not live up to our expectations. This was only a temporary setback as we proceeded with a clinical study of a new implant which had been approved for use in humans. This provided a unique insight into clinical research. I got the opportunity to follow patients all the way from inclusion to final follow-up. I learned how to direct and organize a clinical trail from start to end.

By the time the clinical study was completed, I had become a specialist in orthopedic surgery. Subsequently, I was offered a position at Aalborg University Hospital in the Orthopedic department in the spine surgery unit, and perhaps even more fortunate, an offer to complete my PhD project in Aalborg. Finally, I conducted a systematic review with my supervisors. This was again a new area of research which provided new knowledge and insight.

The project has been changed along the way with new partners and taken longer than expected. However, all the studies are centered around lumbar disc herniation and improvement of the surgical treatment. I have gained a broad knowledge of research, and equally important learned how essential collaboration is.

ACKNOWLEDGEMENTS

During this PhD project I have received invaluable help from a number of people whom I would like to thank.

My main supervisor Søren Eiskjær, who not only offered me a position in the spine unit, but also without apprehension offered to help me finish my PhD. Together with co-supervisor Peter Heide Pedersen, you showed me confidence and believed in the project. It has been great to do research with you, nothing has been impossible and the standards are high. Thanks to Michael Bendtsen, co-supervisor from Aarhus, for support all the way through.

I would also like to thank the department, particularly my colleagues in the spine unit for a warm welcome. It has been nice to be able to come to you and have a talk about all kind of problems. Thanks to Interdisciplinary Orthopaedics for financing the time for me to finish the thesis. Thank you, all the people, at Aarhus University Hospital who helped me in the first part of the project, especially the staff at Orthopaedic Research Lab and the patients in the clinical trial, thanks for offering your time and participation.

Thanks to Torben Tvedebrink at the Institute for Mathematical Sciences, Aalborg University, for helping with statistics and thanks to Jette Frost at the Medical Library, for assistance with literature search. Bruce Robie, thanks for assistance with the clinical trial and much more. Thanks to Albert Veen and the staff in Amsterdam for an inspiring stay.

Finally, thanks to my wife Sanne, I could never have made it without your endless support.

LIST OF PAPERS

This thesis is based on the three following studies, which will be referred to in the text by their numbers (1-3).

Study 1 Biomechanical evaluation of annulus fibrosus repair with scaffold and soft anchors in an ex vivo porcine model. Rickers K, Bendtsen M, Le DQS, Veen AJ, Bünger CE. SICOT J. 2018;4:38. doi: 10.1051/sicotj/2018020. Epub 2018 Sep 7. PMID: 30192225; PMCID: PMC6128169.

Study 2 Temporary axial rotation stabilization for lumbar disc herniation surgery with the ARO®spinal system: a prospective analysis of safety and clinical efficacy. Rickers KW, Li H, Robie B, Bünger C. J Spine Surg. 2019 Mar;5(1):124-131. doi: 10.21037/jss.2018.12.13. PMID: 31032447; PMCID: PMC6465462.

Study 3 Comparison of interventions for lumbar disc herniation: a systematic review with network meta-analysis. Rickers KW, Pedersen PH, Tvedebrink T, Eiskjær SP. Spine J. 2021 Mar 3:S1529-9430(21)00110-8. doi: 10.1016/j.spinee.2021.02.022. Epub ahead of print. PMID: 33667683.

TABLE OF CONTENTS

THESIS AT A GLANCE

Study 1

Aim: To investigate a novel annulus fibrosus repair using a polycaprolactone scaffold and soft anchors for fixation, with focus on biomechanical performance and the ability to retain nucleus pulposus.
Design: Ex vivo biomechanical testing of an experimental annulus repair in nine porcine spinal motion segments. Flexion-extension, lateral bending, and rotation were investigated with an intact annulus, defect annulus, and repaired annulus. Push-out test was performed to see if the repair could contain nucleus under axial pressure.
Primary outcome: Range of motion, neutral zone, and neutral zone stiffness were compared for the three conditions of annulus. Visual examination of push-out test.
Conclusion: The annulus repair showed promising biomechanical behavior in flexion-extension, lateral bending, and rotation, but was not able to retain nucleus.

Study 2

Aim: To clinically test a novel implant for use in conjunction with discectomy for lumbar disc herniation
Design: A prospective cohort with 20 patients.
Primary outcome: Safety in the form of adverse events. Secondary outcome was patient reported outcome measures.
Conclusion: The implant did not increase the risk of surgery. The reoperation rate was 5% at 1-year follow-up.

Study 3

Aim: To compare all current surgical treatments for lumbar disc herniation.
Design: A systematic review with network meta-analysis.
Primary outcome: Leg pain VAS score, functional score, and reoperation rate after 1 year compared between treatments and ranking of the treatments.
Conclusion: Most of the investigated treatments performed very similar. Percutaneous discectomy and conservative treatment were inferior to standard-, tubular-, and endoscopic discectomy.

ENGLISH SUMMARY

Partial discectomy is an effective treatment for lumbar disc herniation in cases where the radicular pain does not subside after 6-12 weeks. The procedure can be performed on an outpatient basis and rapid pain relief can be expected. Unfortunately, 6-18% need revision within the first few years due to reherniation. Part of the reason for this is presumably that the operation simply removes the herniation and does not address the underlying cause, the degeneration of the intervertebral disc. Consequently, intensive research is being done into methods partly to avoid reherniation, but also more advanced treatment aimed at regenerating the intervertebral disc.

The goal of this PhD project was to investigate new methods of treating disc herniation. The dissertation is based on three separate studies. All three studies have been published in international peer-reviewed journals.

The first study was an ex vivo study examining the biomechanical properties of a new experimental bio scaffold for the repair of the annulus fibrosus. Nine porcine spinal motion-segments were used for the purpose, where movement patterns before and after the repair were examined. Furthermore, it was tested whether the repair could withstand pressure in the axial direction. The results showed that the movement patterns were restored, but the repair failed the push-out test.

Study 2 was a clinical study examining the safety and efficacy of a new implant. The purpose of the implant was to create temporary axial rotational stability in conjunction with surgery for lumbar disc prolapse. A cohort of 20 patients underwent surgery and had the new implant inserted. We found no increased risk associated with the implant after one year. However, it was not possible to estimate the effectiveness in such a small study with this design.

The third study was a systematic review of previous studies comparing current treatments for lumbar disc reherniation, including new treatments with annulus repair and dynamic stabilization. Change in pain and function, as well as the reoperation rate were compared between 32 studies. The different surgical techniques performed very similarly, however, percutaneous discectomy and conservative treatment performed inferior to the others.

The development of a new treatment or new implant from idea to approved product is a complicated process with many steps. Although this PhD project has not resulted in a completely new treatment, many of the processes have been completed and an evaluation of the current treatments has been carried out.

DANSK RESUME

Partiel diskektomi er en effektiv behandling ved lumbal diskus prolaps i de tilfælde, hvor de radikulære smerter ikke fortager sig efter 6-12 uger. Indgrebet kan foretages ambulant, og der kan forventes hurtig smerte lindring. Desværre behøver 6-18% revision inden for de første par år grundet reprolaps. En del af årsagen hertil er formodentlig, at man ved operationen blot fjerne prolapsen og ikke adresserer den tilgrundliggende årsag, degenerationen af intervertebral disken. Følgelig forskes der intensivt i metoder dels for at undgå reprolaps, men også mere avanceret behandling som sigter efter at regenerere intervertebral disken.

Målet med denne ph.d. var at undersøge nye metoder til behandling af diskus prolaps. Afhandlingen bygger på tre separate studier. Alle tre artikler er blevet publiceret i internationale peer-reviewed tidsskrifter.

Første studie var et ex vivo studie som undersøgte de biomekaniske egenskaber af et nyt eksperimentelt bio scaffold til reparation af annulus fibrosus. Ni ryg-bevægesegmenter fra grise blev benyttet til formålet, hvor bevægelsesmønstre før og efter reparationen blev undersøgt. Yderligere blev det testet om reparationen kunne holde til tryk i aksial retning. Resultaterne viste at bevægelsesmønstrene blev genoprettet, men reparationen holdt ikke til tryk-testen.

Studie 2 var et klinisk studie som undersøgte sikkerheden samt effektivitet af et nyt implantat. Formålet med implantatet var at skabe midlertidig aksial rotations stabilitet i forbindelse med operation for lumbal diskus prolaps. En kohorte på 20 patienter blev opereret og fik indsat det nye implantat. Efter et år viste det sig at der ikke var øget risiko forbundet med implantatet. Det var dog ikke muligt at estimere effektiviteten i så lille et studie med dette design.

Tredje studie var en systematisk gennemgang af tidligere studier som sammenlignede aktuelle behandlinger af diskus prolaps, inklusive nye behandlinger med annulus reparation og dynamisk stabilisering. Ændring i smerte og funktion, samt reoperations-raten blev sammenlignet i 32 studier. De forskellige kirurgiske teknikker præsterede meget ens, perkutan discectomi og konservativ behandling klarede sig dog ringere end de andre.

Udviklingen af en ny behandling eller nyt implantat fra idé til godkendt produkt er en kompliceret proces med mange trin. Selvom dette ph.d.-projekt ikke har resulteret i en helt ny behandling, er mange af processerne blevet gennemført, og der er foretaget en systematisk evaluering af de aktuelle behandlinger af lumbal diskus prolaps.

ABBREVIATIONS

IVD	Intervertebral Disc
IDD	Intervertebral Disc Degeneration
AF	Annulus Fibrosus
PCL	Polycaprolactone
LDH	Lumbar Disc Herniation
RCT	Randomized Controlled Trials
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
AE	Adverse Events
SAE	Serious Adverse Events
CRO	Clinical Research Organization
PROM	Patient Related Outcome Measures
VAS	Visual Analog Scale
ODI	Oswestry Disability Index
EQ5D	EuroQol 5D
JOA	Japanese Orthopedic Association Score

CHAPTER 1. BACKGROUND

Spinal disorders and sciatica have been known since ancient times. In 1864 Laségue made a thorough description of sciatica and named the straight leg test as sign of an acutely compressed nerve root (1, 2). In 1934, Mixter and Barr were the first to perform partial discectomies in patients with lumbar disc herniations (3). Since then, partial discectomy for lumbar disc herniation has become one of the most frequently performed spine procedures.

1.1. PATHOLOGY

Lumbar disc herniation is a consequence of degenerative disease in the lumbar spine. The herniation occurs when the nucleus pulposus is pushed out through a tear in the annulus fibrosus. Despite the often-acute onset, disc herniation is a disease most commonly preceded by intervertebral disc degeneration a condition which has developed over a long period of time. The pathogenesis of intervertebral disc degeneration is much disputed. As the intervertebral disc is avascular, nutrient supply happens by diffusion. An association between reduced blood flow to the margins of the intervertebral disc and the degree of degeneration has been observed several times (4, 5). This leads to the hypothesis that degeneration is due to lack of oxygen or nutrients (6), but this has still to be proven. Boos et al have described increasing degenerative histological changes with increasing age (7). Endplate and nucleus pulposus are the first to be significantly affected at the end of the first decade. In the second decade changes also affect the annulus fibrosus. Almost all human intervertebral discs have substantial signs of degeneration at age thirty. The integrity of annulus fibrosus is compromised along with the degeneration (8). The number of lamellae is decreased and the organization weakened, leading to annular tears (9). The exact cause leading to the nucleus pulposus being pushed out is unknown.

The herniated nucleus pulposus frequently cause neuropathic pain corresponding to the dermatome supplied by the nerve. It is allegedly not the pressure on the neural axons itself, but the ischemia that occurs that is attributed to the pain reaction (10). Experimental investigations have shown that ligation of a nerve alone is not enough to cause pain (11). Not only the mechanical pressure on the nerve, but also a biochemical reaction triggered by the ruptured disc is believed to cause the painful symptoms. Nucleus pulposus initiates a painful inflammatory reaction, when pushed out of the intervertebral disc space (12, 13).

The cause of back pain is still not fully elucidated. In the case of lumbar disc herniation, however, there is much to suggest that pain originates from the intervertebral disc, more specifically the nerves in the outer part of the annulus fibrosus (14).

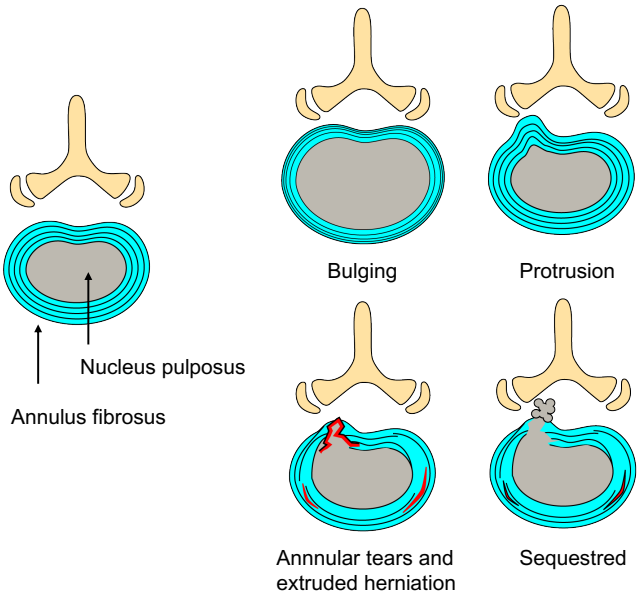


Figure 1. When the disc degenerates the annulus deteriorates, this can cause bulging or protrusion. Disruption of the annulus creates tears through which the nucleus can herniate.

1.2. CLINICAL FEATURES AND DIAGNOSIS

Although the symptoms vary a lot, patients often report back pain in the prodromal period, changing into radiating leg pain after a while. Patients report both prior traumatic episodes as well as spontaneous onset of symptoms. The majority experience improvement of symptoms within 6-12 weeks, and gradual remission without the need for treatment. However, 10-20% have persistent symptoms and undergo surgery (15).

Examination of the patient includes patient history, clinical examination including neurological examination with a focus on sensory and motor function in the lower extremities and deep tendon reflexes. Magnetic Resonance Imaging is the gold standard for diagnostic imaging for lumbar disc herniation diagnosis, supporting the clinical diagnosis. It is precise, widely available and non-harmful for the patient. The advantages compared to CT and myelography is better visualization of soft structures, especially outside the dural sack. Disc herniations can be asymptomatic (16, 17), accordingly is it important that there is a clear connection between patient reported

symptoms, the clinical examination, and MRI findings. Different classifications have been developed to aid when describing herniations on MRI (18, 19).

1.3. PREVALENCE

Spinal disorders are very frequent among the general population and have a huge impact on society. The actual frequency of lumbar disc herniation is difficult to assess, as it is often only cases that require surgery that are registered. A report from the Finnish Social Security from 1988 estimated a frequency of 1-3% in the entire population (20). The DaneSpine annual report 2018, state that 2582 patients were operated for lumbar disc herniation in Denmark that year (21). The average age was 47 years, and the gender ratio was 56/44 men/women. Visual analog score for leg pain preoperative and 1-year post-operative were 58 and 25 (0-100 scale) respectively (21).

Since it often affects the middle-aged part of the population, and extends over a longer period of time, it diverts a number of days for sick leave, an estimated 20% of all sick leave can be attributed to low back pain (22). The socio-economic impact is extensive, although difficult to estimate (23).

Genetics has been shown to be an important factor in disc degeneration. Twin studies support this and the fact that hard work and wear and tear are not as important as previously thought (24). However, strenuous activities are risk factors for lumbar disc herniation, this was seen in Copenhagen Male Study, just as the study also showed that smoking also is a risk factor (25).

1.4. CONSERVATIVE TREATMENT

In 2016, The Danish National Clinical Guidelines for Non-surgical Treatment of Recent Onset Lumbar Nerve Root Compression was published (26). The evidence behind a wide range of conservative treatments was assessed and recommendations were made based on this.

Bedrest is no longer recommended as before. This is based on two RCTs which could not prove any difference on maintaining normal activity and bedrest for two weeks (27, 28).

Physiotherapy and chiropractic were also reviewed. There is no solid evidence to support the use of these treatments. Nevertheless, like many similar countries, the guidelines chose to make a weak recommendation for this treatment.

Steroid injections, either epidural or periradicular via transforaminal access are also used as conservative treatment. Here, again, the evidence is weak. A systematic review including 38 studies found that the effect was small and unsustained (29). It can be an alternative to surgery if the patient declines surgery or is not fit for surgery.

The majority of patients are initially treated with medication from their general practitioner. Despite this, there is not much literature on the effects of medical treatment. Non-steroid-anti-inflammatory-drugs have an effect on back pain whereas the effect on radicular pain is doubtful (30). The effect of opioids and anti-epileptic drugs on radicular pain has only been sparsely studied, and these drugs should be used with caution as there are a number of side effects (31).

1.5. SURGICAL TREATMENT

If progressive neurological symptoms or cauda equina occur, there is an absolute indication for surgery that should be performed as soon as possible to avoid permanent neurological damage (32).

Surgery to relieve pain is a relative indication and is much debated. However, it has gradually been accepted that surgery is favorable in cases where conservative treatment has failed and severe symptoms persist after 6-12 weeks, and a strong agreement between clinical findings and MRI findings exists. The major benefit is fast relief of sciatica. A number of studies support this.

One of the first large RCTs investigating surgery for lumbar disc herniation was conducted by Weber et al in 1983 (33). In this trial surgically treated patients reported significantly higher patient satisfaction than in the non-surgically treated group. However, this difference diminished over time, so that after four years, the difference was no longer significant.

The Maine Lumbar Spine Study was a non-randomized cohort which compared surgical with non-surgical treatment of lumbar disc herniation (34). This study also favored surgery with a maximum difference between the treatments at two years (35).

A major challenge in the RCTs investigating treatment of lumbar disc herniation is a high rate of cross over. This phenomenon is seen in two large RCTs, Weinstein et al (36) and Peul et al (37). Neither of these studies could prove a difference in patients treated with surgery compared to non-surgery. But in the former study, a parallel observational cohort showed superior results with surgery (36). In the latter, a subsequent cost-utility analysis showed that the patients who underwent surgery early in the course returned to work faster and had less pain than those who underwent surgery later (38).

It seems clear that discectomy for lumbar disc herniation to the right patient is an effective treatment. However, it is still not entirely clear which patients benefit the most from surgical treatment and which technique is the best.

1.6. SURGICAL TECHNIQUES

There are several surgical techniques for lumbar disc herniation. The surgical method first described is still the most popular, standard open surgery. Advantages of this method are good visualization of the nerve and herniation and the fact that it is an approach that spine surgeons are familiar with. The introduction of loupe glasses and the operation microscope allowed for a smaller approach and better visualization. Microdiscectomy/open discectomy are considered the golden standard in surgical treatment of lumbar disc herniation (39, 40).

Spine surgery has been involved in the development of minimally invasive surgery (MIS) from early on, many spine surgery procedures can be performed as MIS. The MIS version of the discectomy is performed with a paramuscular approach as described by Smith and Foley in 1998, (41), and uses a tubular retractor of about 20mm in diameter. An operating microscope and special MIS instruments can be used with advantage. The advantage of MIS is supposedly less trauma and shorter rehabilitation (42). The less invasive procedures have made it possible to perform the surgery on an outpatient basis.

Endoscopic discectomy has been in use since the 1990s. The method primarily uses two approaches. The translaminar paramuscular approach and the transforaminal approach. The latter is a modification of the approach originally described by Wiltse for reaching far-lateral herniations (43). Kambin described the technic in 1986 and the safe spot for accessing the disc was named after him (44).

Lindholm first described discography in 1948 (45). It utilizes a posterolateral approach with the aid of fluoroscopy. The same technique is used in percutaneous discectomy (46). This procedure differs from the previously mentioned in that it is not aimed at removing the herniation, but at relieving the pressure in the disc. A variation of techniques to achieve this, have been developed: nucleotomy, intradiscal electrothermal therapy, and nucleoplasty, among others. Although still in use, these methods are considered to be inferior to the above-mentioned methods (47).

Chemonucleolysis has been used with the same technique as percutaneous discectomy. Instead of mechanically removing nucleus pulposus, it is dissolved by a chemical substance. It has become obsolete due to allergic reactions towards the substances used, incidences of transvers myelitis, and inferior clinical results (48).

Biological treatment targeting tumor necrosis factor has also been investigated. A systematic review from William et al, concludes that there is currently not enough evidence to recommend biological treatment, and they suggest that larger RCTs be performed (49). The authors later tried to set-up an RCT, which unfortunately did not succeed. There is still no evidence to offer biological treatment.

In a study offering fusion together with discectomy, it was found that there was a lower frequency of reherniation (50). However, it requires full interbody fusion to achieve this. Dynamic stabilization has been attempted as adjunct in discectomy but its significance is uncertain (51).

Challenges with many reherniations and reoperations have caused an increased focus on repairing the defect in the annulus fibrosus. Often the surgeon faces a dilemma of either doing an aggressive discectomy to prevent the remaining nucleus pulposus from creating a reherniation, or leaving some of the nucleus pulposus behind to prevent accelerated disc degenerating (52). An obvious solution seems to be a simultaneous repair of the annulus which will avoid reherniation and at the same time prevent further disc degeneration. Very different solutions have been proposed, ranging from advanced regeneration of the intervertebral disc itself with stem cells and tissue engineering (53) to simple mechanical closure of the defect (54). Methods including stem cells are still very experimental whereas simple repair methods are being tested in clinical trials.

1.7. OUTCOMES

The studies that have examined the effect of discectomy have shown that there is a variation of the results for the individual patients. Some patients seem to benefit more from surgery than others. This fact has resulted in a search for useful predictors for satisfactory patient reported outcomes.

One important factor much disputed is the timing of surgery. While it is generally accepted to wait 6-12 weeks before surgery, it is more unclear how long it is possible to wait before it negatively affects the results. A systematic review examining the optimal timing found that longer symptom duration had an adverse impact on the outcome (55). However, there still seems to be an effect of surgery even after prolonged symptoms. Bailey et al (56) investigated if surgery beyond 4 months of symptom onset had any effect. They conducted a RCT with discectomy versus conservative care, which included patients who have had sciatica between 4 and 12 months. They found discectomy to be superior to non-surgical care. The presence of neurological deficit remarkably does not appear to influence the outcome, while the severity of symptoms does (57).

Herniation morphology is probably also of significance. Carrage et al (58), found that a large annulus defect was associated with a higher probability of reherniation and reoperation. This is consistent with a study by Miller et al (59), who also found that a high rate of reherniation correlated to a large annulus defect. The location of the herniation did not seem to have any influence on the result (60).

In addition to biological conditions, psychological and social conditions also affect the course of the disease. One of the strongest predictors of getting back into the job

market is the length of sick leave before surgery. A period longer than 3 months of sick leave significantly reduces the probability of returning to work (61). Psychological condition, however, appears to be the most significant factor influencing the outcome, more significant than symptom severity, MRI findings, and neurological status (62). According to Sørensen et al. the psychological profile of the individual patient had a profound influence on the outcome of surgery for herniated disc (63).

1.8. COMPLICATIONS

The usual complications of surgery also apply to discectomy and with approximately the same frequency. Wound infections, worsening of neurologic deficits, and lesions of the dural sac occur in 1-3% of patients (64). But in addition, there is a fairly large group of patients who must undergo surgery again due to reherniation. The actual reherniation rate is difficult to estimate as reherniation can be defined in a multitude of ways. However, the frequency of reoperations due to reherniation within the first year has been reported up to 7-18% (65-67). This makes reherniation the most frequent complication, next after no effect of surgery. Reherniation after surgery has been associated with large annulus defects (59), limited nucleotomy (instead of aggressive) (67), sex, age, and body mass index (68, 69). However, an US retrospective survey including approximately 30,000 patients found a slightly more optimistic result, which showed that 6% received a reoperation, for a variety of reasons including reherniation, within the first year (70).

CHAPTER 2. STUDY AIMS AND HYPOTHESES

Aims

Study 1 Aimed to test a new annulus repair method using a PCL scaffold and soft anchors. Biomechanical testing was performed to see if the method was compatible for use in conjunction with surgery for lumbar disc herniation.

Study 2 Aimed to evaluate the safety and effectiveness of an implant providing axial stability in patients undergoing decompression surgery for lumbar disc herniation in a clinical trial.

Study 3 Aimed to conduct a systematic review of RCTs treating lumbar disc herniation and perform a network meta-analysis to be able to rank the treatments.

Hypotheses

Study 1 A PCL scaffold with soft anchors will be able to close a defect in the annulus fibrosus, will be able to withstand a push-out test, and not deteriorate the biomechanical properties of the spinal motion segment tested.

Study 2 Patients receiving the implant will have the same or less complications compared to patients receiving standard open discectomy. Efficacy will be the same or better.

Study 3 A systematic review with a network meta-analysis will be able to rank the existing surgical treatments with respect to pain relief, improvement in functional score, and reoperation rates.

CHAPTER 3. METHODOLOGICAL CONSIDERATIONS

It is to a great part the research question that determines which design should be used to be able to answer the scientific question. Different methodological designs were used in the three studies, on which this dissertation is based.

3.1. STUDY 1 - BIOMECANICAL TESTING

The first study examined the feasibility of using a scaffold and sutures for annulus repair. The biomechanical impact and the ability to withstand a push-out test was tested in an animal ex vivo model. The new experimental repair method was developed in collaboration with The Interdisciplinary Nanoscience Center at Aarhus University. The test was performed at Vrije Universiteit, Amsterdam, as they had the necessary test equipment.

3.1.1. INTERVENTION

A combination of closing the defect with a scaffold made of biomaterial and suture was chosen as repair method.

"Scaffold", is a term used in tissue engineering for a structure to support cell growth. It is often made of biomaterials and has a porous design. Depending on the design the scaffold can inherit different properties, for example the ability to release drugs or seed and grow cells on it prior to use.

Fabrication of the scaffold was done at the Interdisciplinary Nanoscience Center at Aarhus University. The scaffold design was a modification of a scaffold previously used for in vitro test of mesenchymal cell growth (71).

The biomaterial used was polycaprolactone which degrades into lactic acid over time. Polycaprolactone is a very elastic material, and depending on the pattern of printing, the resulting mechanical properties will differ. A mat with layers of 200 um thick PCL fibers on top of each other was 3D printed. Fibers in consecutive layers were angled 60 degrees to mimic the layers in the annulus fibrosus. Cylinders were cut out of these mats with a diameter of 4 mm and a heigh of 8 mm. To improve cell growth, the surface area was increased by treatment with dioxane and ethanol/water, furthermore the surface was made more hydrophilic by NaOH treatment. The result can be seen in scanning electron microscope. Figure 2 illustrates this.

To secure the scaffold in AF, two soft anchors (Juggerknot 1.4mm, Biomet®) were used, one inserted in each vertebra cranial and caudal. The scaffold was accordingly pressed into the defect and then fixed by the sutures from the soft anchors, see Figure 3.

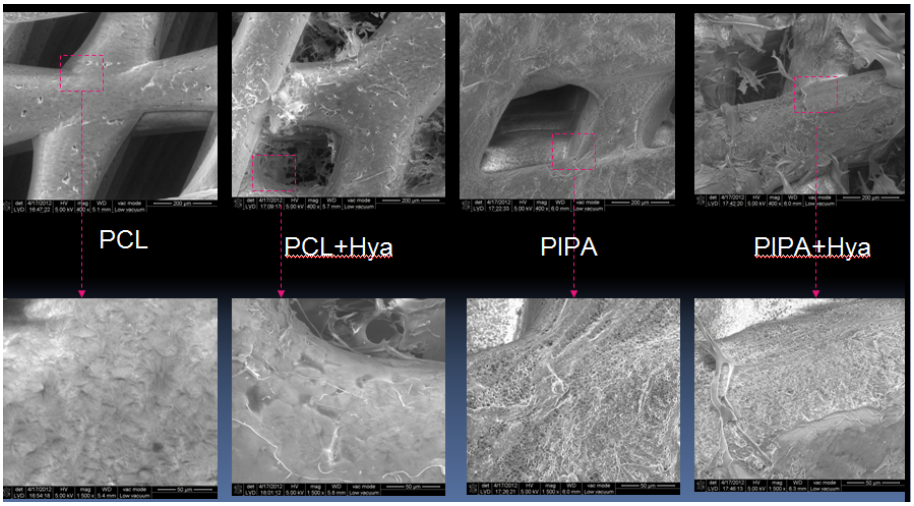


Figure 2. SEM image of the scaffold used for AF repair. PCL , pure polycaprolactone. PCL+Hya, PCL treated with NaOH. PIPA, PCL treated with dioxane. PIPA+Hya, PCL treated with both dioxane and NaOH.

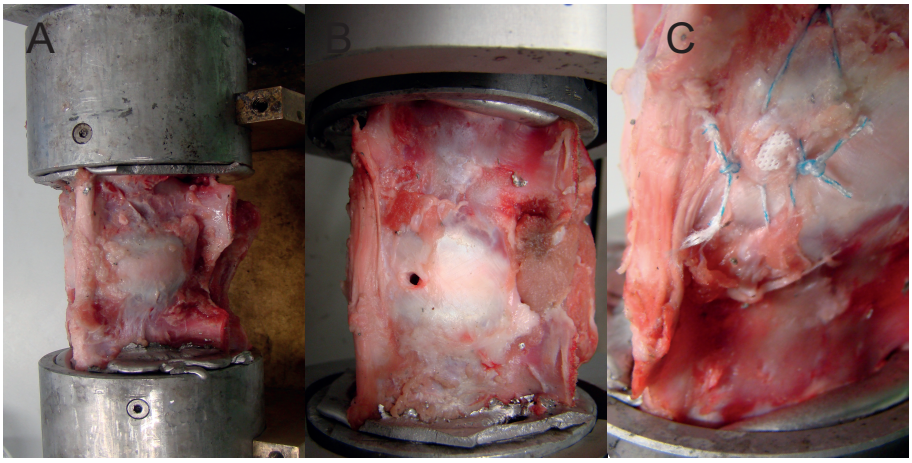


Figure 3. Showing the three conditions examined. A, native; B, with the defect in annulus; C, with the annulus repair. Load-deflection test was repeated for all three conditions. Figure from paper 1 (72)

3.1.2. ANIMAL MODEL

Porcine lumbar spines were obtained from a local abattoir. The specimens came from 40 kg landrace pigs. L1-L6, spinal vertebrae, were harvested and frozen until the day before use, when they were slowly thawed. With a fine saw, the spines were divided into motion segments. All muscles and tendons were removed. The joint capsule and ligaments remained intact. The ends of the motion segments were embedded in low melting point bismuth alloy and mounted into a custom-made jig, this to insure absolutely no slack during testing.

The defect was made antero-laterally in the annulus fibrosus with a 3mm biopsy punch (Miltex, Japan), cutting out a full thickness annulus biopsy. This left a 3 mm circular hole with the nucleus pulposus visibly protruding when manipulated. Nucleus pulposus was left untouched in the disc space. To avoid any drying or creeping of the specimens they were kept moist with isotonic saline.

3.1.3. TEST SETUP

Nine motion segments with nine scaffolds were tested. The jig with the spinal motion segment was mounted in the test machine, an Instron 8872 (Instron Corp., Norwood, MA), Figure 4. The test was performed three times on each motion segment, first with the intact annulus, secondly the defect was applied and finally the annulus was repaired and the last test was performed. All three tests included flexion-extension, lateral bending, and rotation. The motion segment was applied a maximum moment of 2Nm with a frequency of 1 degree pr. sec.

In the beginning of the test, tissue behavior can vary greatly due to hysteresis, by running 10 loading cycles equilibrium is achieved and the effect of hysteresis is minimized.

Load-deflection data were obtained and subsequently plotted in a graph. Range of motion is readily acquired from the graph and as shown by Smit et al (73), neutral zone and neutral zone stiffness can also be calculated from this graph.

Finally, a push out test was performed as the last test, since this can destroy the test specimen. Axial compression was applied until the scaffold was pushed out or any other sign of failure. A camera, synchronized with the test equipment, was recording in order to establish the precise moment of failure.

Data was handled as a random sample from a normal distribution. Differences (paired) were independent and from same distribution. Groups were compared by t-test and means. P-values less than 0.05 were considered significant.

Figure 4.

The biomechanical test setup in Amsterdam. The servo hydraulic machine affects the jig where the motion segment is mounted, data is transferred to the computer.

3.2. STUDY 2 - CLINICAL TRIAL

The implant investigated in this study came from a collaborator from the US, who invented this implant. It had been through comprehensive biomechanical testing and was ready to be evaluated in a clinical trial. The clinical trial was done at Aarhus University Hospital from 2013 till 2016. The trial was monitored by an external company, Larix, Ballerup, a clinical research organization (CRO).

The study was designed as a prospective cohort study, and was approved by the local ethics committee. Registration was done at www.ClinicalTrial.gov. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Guidelines from STROBE (74) were followed in reporting the study.

3.2.1. STUDY POPULATION

Included patients were referred from general practitioners. Patients were then seen in the outpatient clinic for examination and anamnesis.

Inclusion criteria for participants:

- Between 18 and 55 years of age at time of consent.
- Had a primary one-level posterolateral herniation in the lower lumbar spine (L4-L5 or L5-S1 only) as shown by magnetic resonance imaging (protrusion, extrusion or sequestered fragment) consistent with the clinical symptoms (both with regards to level and side of LDH).
- Had radicular pain and evidence of nerve-root irritation lasting 6 weeks or more as evidenced by both radicular pain below the knee and sign of nerve root irritation. Positive straight leg raise test, femoral tension sign, or neurologic deficit was considered sign of nerve root irritation.
- Confirmed by the investigator to be a surgical candidate for discectomy.
- Scheduled for their surgical procedure no more than two months from the time of consent.
- Willing to complete the study requirements and permit agency and sponsor authorized personnel to access medical records.
- Able to understand oral and written Danish.

Exclusion Criteria were

- Previous lumbar surgery.
- Cauda equina syndrome.
- Scoliosis greater than 15 degrees.
- Osteoporosis.
- Segmental instability (>10degrees angular motion or >4mm translation).
- Vertebral fractures.
- Spinal infections.
- Spinal tumors.
- Inflammatory spondyloarthropathy.
- Pregnant or the intent to become pregnant in the following year.
- Comorbid conditions contraindicating surgery.
- Multiple herniations.
- Known allergy to titanium, aluminum or vanadium.
- Female patients of childbearing age who were not willing to use adequate contraception.
- Patients who refused research participation were also excluded

Above text describing the criteria is from paper 2 (75).

Patients were to have lumbar disc herniation seen on MRI together with radicular pain in the corresponding dermatome to be candidates for surgery. Information about the procedure and expected outcome were discussed with the patient. If the patient chose surgery, they were also offered to participate in the clinical trial.

The upper age limit was set to avoid patients where spondylosis and stenosis were the cause of the symptoms, moreover, it corresponds to the typical age of patients with lumbar disc herniation.

Fardon et al (19) was used to classify disc pathology on MRI. X-ray were used to evaluate scoliosis and segmental instability.

Many of the exclusion criteria were set to have a homogeneous group similar to the typical herniation patient such as no previous surgery or fractures, no scoliosis or segment instability.

3.2.2. INTERVENTION

The implant was designed to provide temporary axial stability in a lumbar spinal motion segment in combination with discectomy. The system is composed of an anchor, placed in the pedicle on the side of the herniation, and a button at the spinous process on the contra-lateral side. The anchor and button are joined with a commercially available high strength suture (MaxBraid, Biomet). The implant system

is inserted in alignment with the disc, and crosses the disc of the treated level. When completed, the suture tethers the upper vertebral body to the lower to resist axial rotation of the upper vertebral body with respect to the lower body.

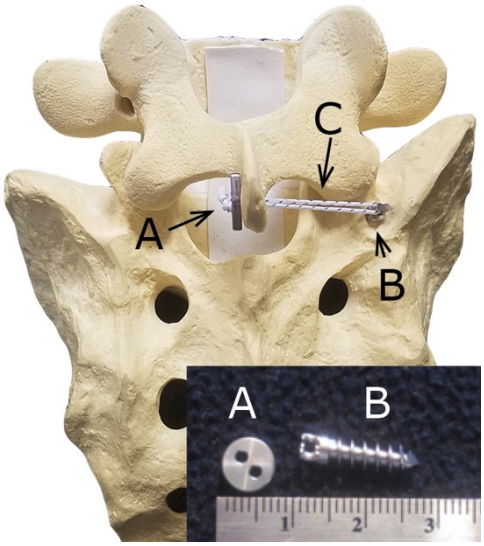


Figure 5. The implant providing temporary axial stabilization shown on a saw bone. A, button placed on the contra-lateral side of the herniation, the knot is tied on this; B, screw placed in the pedicle on the side of herniation, the wire runs through this; C, the wire. Figure from paper 2 (75).

The implant was only used on the side of the disc herniation (paramedian). The reason for this was that it has been shown that the highest strain on the AF is on the contra-lateral side of the movement. That is, when the spinous process moves away from that side of the herniation, the highest strains in AF fibers is on the herniation side. This has previously been shown in a Finite Element Analysis(76). In addition, you avoid having to expose both sides.

The anchor and button are composed of titanium which is biocompatible (77) and has been used for many years as screws, plates and implants in general. The suture is made of Ultra High Molecular Weight Polyethylene (UHMWPE), also a well-known material.

Patients were prepared as for standard open discectomy. General anesthesia was used and the patients were positioned onto a radiolucent table prone on two horizontally placed padded bolsters. Antibiotics were administered preoperatively. Fluoroscopy

were used to identify the level and a translaminar approach was used. The descending nerve was kept away and the herniation removed. The anchor was inserted in the lower vertebral pedicle. The spinous process was perforated with a small drill for the suture. The suture was then passed from the contra lateral side through the hole, passed through the eye in the anchor and back through the spinous process. Both ends were passed through the button and used to tie a knot. The knot was tightened with 75N using a custom-made suture tightener. Standard wound closure procedure was used, patients received standard post-operative care.

3.2.3. OUTCOMES

As this were the first clinical use of the implant, focus was on safety. ICH Harmonized Tripartite guidelines, originally aimed at pharmaceutical clinical trials, but also applicable on clinical trials involving implants, define serious adverse events (SAE) as death, life threatening condition, hospitalization or prolonging of hospitalization, and persistent or significant disability/incapacity. Occurrence of an SAE initiated a contact to the CRO, who informed the Danish Medicine Agency within 24h. All adverse events were also registered for the final report.

Anterior-posterior and lateral X-rays were obtained post-operatively, and at 6 and 12 months and evaluated for any change in implant position or other abnormality.

Intraoperative estimated blood losses, surgery times, and incidences of dural tears, dural hematomas, and post-operative infections were recorded.

Secondary outcomes were patient related outcome measures (PROM). These included patient-reported visual analog scale (VAS) for leg and back pain, Oswestry disability Index (ODI) was used for functional outcome, to measure general health status EuroQol 5D (EQ5D) was used, finally patients were asked how satisfied they were with the result. Additionally, neurological status was examined at each follow-up. Follow-up intervals are seen in Table 1.

Table 1. Schedule for patient follow-up.

Assessment	Preoperative (within 2 months of surgery)	Operative	6 weeks ± 2 weeks	3 months ± 2 weeks	6 months ± 2 weeks	12 months ± 2 weeks
Inclusion and Exclusion Criteria	X					
Medical History	X					
Pregnancy Test (Female Only)	X					
Demographic Data	X					
Adverse Events		X	X	X	X	X
Anterior-Posterior X-Ray (for Safety)	X				X	X
Medial-Lateral X-Ray (for Safety)	X				X	X
VAS-Back	X		X	X	X	X
VAS-Leg	X		X	X	X	X
ODI	X		X	X	X	X
EQ-5D	X		X	X	X	X
Patient Satisfaction with Symptoms	X		X	X	X	X
MR of Annulus	X				X	X
MR of Facets	X				X	X
MR of Disc	X				X	X
Health Care Utilization		X	X	X	X	X

Table from paper 2 (75).

3.3. STUDY 3 - SYSTEMATIC REVIEW

In the hierarchy of evidence, we find systematic reviews in the top. By collecting available evidence, assessing the quality and synthesizing the results, an overview of the subject is made. Because of this, recommendations and decisions are often based on systematic reviews. To strengthen the quality of systematic reviews a number of guidelines has been developed. Cochrane Collaboration is behind many of these, and has a comprehensive handbook for conducting a systematic review with network meta-analysis, which has been consulted many times in making of this review. PRISMA-P (78) guidelines have been followed and the protocol registered at Prospero (CRD42020210201).

3.3.1. LITERATURE SEARCH

Before embarking on the literature search it is important to set the framework for the review. If it is not clearly defined what is to be investigated and which studies are to be included, this will give rise to problems later. As suggested by Cochrane, the PICO method can be used to set the premises for the literature search.

The letters in PICO are acronyms for four questions that needs to be defined. P - Patient or population, what are the characteristics of the patients or the problem to be investigated? I – Intervention, which intervention is under evaluation? C – comparator, what will the intervention be compared to? O – outcome, which outcomes are relevant?

An example of PICO search strategy is seen in Table 2. The full search strategy used for the review with PICO search terms, Mesh terms, and appropriate operators is included in the appendix.

Table 2. PICO search.

Patient	**I**ntervention	**C**omparison	**O**utcome
Lumbar disc herniation Slipped disc Intervertebral disc displacement Disc prolapse Disc herniation Herniated disc	Discectomy Percutaneous discectomy Endoscopic discectomy Microdiscectomy Annulus closure device Annular repair Implant	Same as intervention	VAS ODI Reherniation Reoperation Resurgery Recurrent

In 2007 a large Cochrane review investigating surgical treatment of lumbar disc herniation was published (39). The literature search used for the Cochrane review overlaps the search performed for this review. It was therefore possible to combine the results and only extend the search back to 2007.

A manual search for relevant studies to include was also performed. Using a similar PICO strategy as before mentioned, a search for relevant reviews was conducted. The reviews found were then searched for relevant studies to include or other papers that could lead to studies which could be relevant to include.

Only peer-reviewed journals in the language of English, Danish, Norwegian, and Swedish were considered. Moreover, is it necessary to decide which study designs to include. Fortunately for this review there were an abundance of RCTs. Studies were also to have a minimum follow up of one year.

A librarian from the Medical Library at Aalborg University assisted with the search strategy and performed the actual online search for both RCT studies and the search for reviews. Databases searched were PubMed, Embase, and Cochrane Library. The search was executed March 2020.

3.3.2. STUDY SELECTION AND DATA EXTRACTION

There are various software solutions to keep track of the large number of studies from a literature search. Endnote X9 (Clarivate, Philadelphia, PA) was used to remove duplicates and update meta-data. For abstract screening and full text review, an online solution from Covidence (Veritas Health Innovation, Australia) with an app for smartphones was used.

Abstract screening was performed individually by at least two reviewers. Two concordant votes were required to proceed to full text review. In case of disagreement, a third reviewer was consulted. The same procedure was used for full text review to decide on the studies to include in the review.

Only studies including patients with primary lumbar disc herniation were considered, leaving out studies concerning subtypes of herniations, such as reherniation, axillary herniation, or herniation on a specific level.

Interventions in question, were all treatments considered as currently widely practiced methods:

OD	Standard Open Discectomy
MD	Microscopic Discectomy
TD	Tubular Discectomy
PD	Percutaneous Discectomy
PED	Endoscopic Discectomy
AF	Discectomy with AF repair
OD_ds	Discectomy with Dynamic Stabilization
Cons	Conservative Treatment

These treatments were additionally considered as comparators, as the intention was to compare them to each other. Conservative treatment was additionally included as comparator.

Three outcomes were chosen for statistical analysis, pain on a visual analog scale, functional score, and reoperation rate.

Visual analog scale for reporting pain is a widely used PROM in spine surgery and reported by the majority of studies, which makes it convenient. In some instances, it is reported for specific regions e.g., leg pain or back pain. In these situations, leg pain was extracted, as it is typically the indicator for surgery.

Different scoring systems for physical function were reported. Most common were Oswestry Disability Index (ODI) and Roland Morris Questionnaire (RM). One study used the Japanese Orthopedic Associations score system (JOA), but different version of this exists. We were not able to identify which version was used and were not able to extract this information.

Many studies report complications such as infection and reherniation rates but often without explanation on how these complications are defined, which makes comparison difficult. Instead, as a measure of complications, reoperation rate was used. Most severe complications will eventually result in a revision, which makes this a valid indicator for complications.

3.3.3. RISK OF BIAS

When the literatures search has been conducted and the studies to be included are identified, assessment of quality is next. To uniform this quality assessment and ensure correct assessment different tools has been developed. In this review risk of bias within the individual studies were assessed using the Cochrane Neck and Back Review Group guidelines (79). These recommend that 5 domains of possible bias

related to the methodology of the study to be investigated by rating 13 questions for each study as either, low risk of bias, high risk of bias, or unsure.

Table 3. Risk of bias assessment.

Source of bias	
Selection	Was the method of randomization adequate?
Selection	Was the treatment allocation concealed?
Performance	Was the patient blinded to the intervention?
Performance	Was the care provider blinded to the intervention?
Detection	Was the outcome assessor blinded to the intervention?
Attrition	Was the drop-out rate described and acceptable?
Attrition	Were all randomized participants analyzed in the group to which they were allocated?
Reporting	Are reports of the study free of suggestion of selective outcome reporting?
Selection	Were the groups similar at baseline regarding the most important prognostic indicators?
Performance	Were cointerventions avoided or similar?
Performance	Was the compliance acceptable in all groups?
Detection	Was the timing of the outcome assessment similar in all groups?
Other	Other potential risk of bias?

3.3.4. STATISTICS

Statistics are used to estimate treatment effects, but equal important examine data and explore the assumptions behind the statistical methods used.

Before the network meta-analysis, data was examined by pairwise meta-analysis which was performed for all three outcomes. This included assessment of heterogeneity using the chi-squared test and publication bias evaluated by using funnel plots. Stata (release 16, Stata- Corp LLC, TX) was used for the pairwise meta-analysis.

Network meta-analysis is a relatively new method that has quickly become popular due to its ability to compare multiple treatments simultaneously.

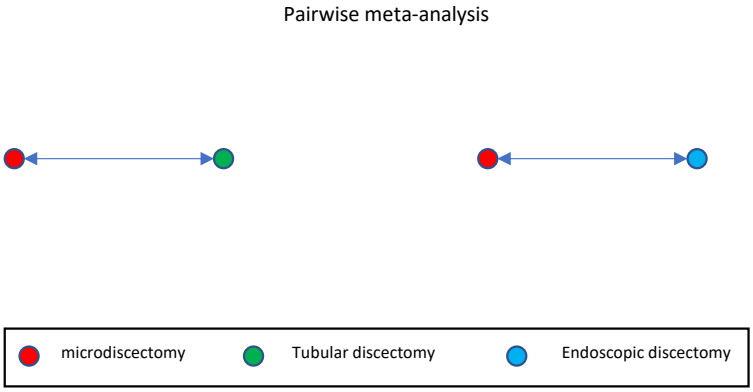


Figure 6. Diagram illustrating relations in pairwise meta-analysis. Only two treatments can be compared in each analysis.

The ordinary pairwise meta-analysis allows only two treatments to be compared at the same time. In the example in Figure 6, microdiscectomy and tubular discectomy. Similar studies that compare the two treatments are found by a literature search and the pairwise meta-analysis makes a pooled effect estimate. A third treatment endoscopic discectomy has in different studies been compared to microdiscectomy. It is, however, not possible with the ordinary pairwise meta-analysis to compare all three treatments in one analysis.

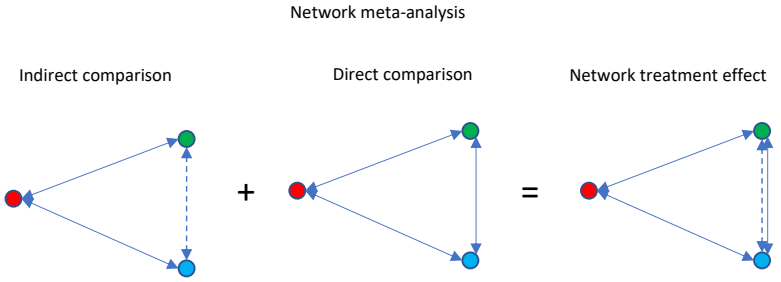


Figure 7. Network meta-analysis allows for multiple treatments to be compared in the same analysis. Direct comparisons are illustrated with solid arrows, indirect comparisons with dotted arrows.

But in the network meta-analysis it can be done. By using a common comparator (microdiscectomy) network meta-analysis allows to estimate the relative efficacy between tubular and endoscopic discectomy, by indirect comparison. Furthermore, if a direct comparison between tubular and endoscopic discectomy exists (studies comparing tubular and endoscopic discectomy actually exits) this can be included in the analysis and synthesize the direct and indirect comparisons to estimate a network treatment effect. Accordingly. the network meta-analysis calculates three different effects. First the indirect one, which is calculated using a proxy, then the direct, which is reminiscent of the pairwise meta-analysis, and finally the network effect which is the direct and the indirect combined. The advantage of this is a more precise estimate by considering all available evidence. Another advantage of network meta-analysis, and perhaps the most clinically relevant, is the potential to more explicitly rank treatments using summary outputs.

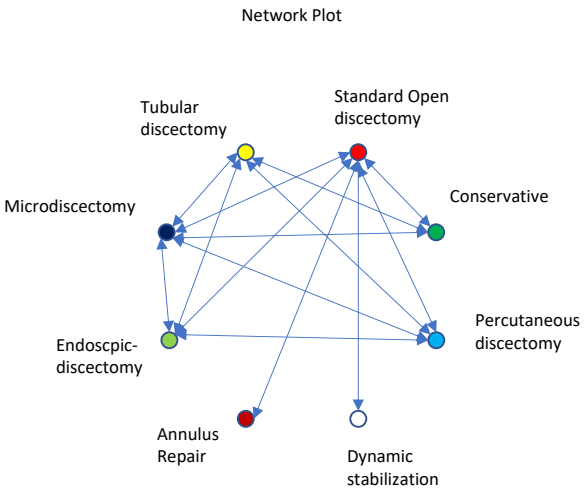


Figure 8. The network plot illustrates all treatments compared and their relations, it can be designed in several different ways depending on what needs to be visualized. Each arrow represents one or more comparisons.

In order to perform this comparison between multiple treatments a number of conditions need to be fulfilled. The RCTs compared must be similar on all important factors, except the interventions. In theory, all patients should be eligible for all trials in the network. This assumption of transitivity is necessary for conducting a network meta-analysis. Transitivity can be assessed by identifying potential effect modifiers such as age, duration of symptoms, preoperative pain score and others; and evaluate their distribution. Meta-regression using these potential effect modifiers will also

reveal if transitivity is violated. Consistency in the network is also a requirement. An exploration of the network is used to evaluate this. Direct and indirect treatment effects should be in statistical agreement, a too large difference indicates something is wrong. Heterogeneity is also a necessity; this is similar to pairwise meta-analysis.

After examination of data, exploration of the network and checking the assumptions, the treatment effects were estimated. Pairwise comparison in the network was performed and treatments ranked, in this study we used the surface under the cumulative ranking curve (SUCRA) to estimate ranking.

Statistical analysis was done in collaboration with the Department of Mathematical Sciences, Aalborg University. Network meta-analysis was done in R version 4.02 using the packages gemtc and BUGSnet (80-82). Transitivity was evaluated by comparing the distribution of effect modifiers throughout the different comparisons by boxplots and with meta-regressions. Node-splitting was used to check for consistency.

The last assessment performed was confidence of the evidence for each outcome. CINeMA web application is a modification of GRADE (Grading of Recommendations, Assessment, Development, and evaluation) made for network meta-analysis to make this assessment (83, 84).

CHAPTER 4. RESULTS

4.1. STUDY 1 - BIOMECHANICAL TESTING

The experiment was performed in two sessions. First part was movement in three directions to obtain load-deflection curves, this was done for the motion segment in native condition, with the defect, and with the annulus repair. Table 4 shows the data from the subsequent analysis of the load-deflection curves. Results in general showed that applying the defect in the annulus deteriorated the intervertebral disc' biomechanical properties. On the contrary, repairing the defect seemed to reverse this effect. This was true for both flexion-extension, lateral bending, and rotation, although not significant in all comparisons.

Second part of the experiment was the push out test which proceeded differently than expected. All the scaffolds in the nine intervertebral discs remained inside the defect until full axial load of 4000N, but the nucleus pulposus leaked out. It proved difficult to determine the exact time, but quite early, at about 300N, it began to seep out between the pores of the scaffold. Based on the results from the push-out test, it was concluded that the scaffold was not suited for annulus repair in, at least in the current design.

Table 4. Result of biomechanical testing.

	Native	**Defect**	**Repaired**
Flexion-extension			
Range of motion (degrees)	5.97(5.01; 6.93)	6.69(5.66; 7.71)*	6.09(5.21; 6.96)†
Neutral zone (degrees)	0.70(0.42; 0. 97)	1.30(0.70; 1.90)	0.84(0.61; 1.07)
Neutral zone stiffness (Nm/degree)	4.38(2.64; 6.12)	6.62(8.71; 28.24)*	6.98(3.53; 10.43)†
Lateral bending			
Range of motion (degrees)	8.39(6.15; 10.63)	8.82(6.62; 11.01)*	8.29(6.14; 10.43)†
Neutral zone (degrees)	1.77(0.42; 3.13)	2.97(0.60; 5.34)	1.95(0.79; 3.11)
Neutral zone stiffness (Nm/degree)	6.68(4.72; 8.64)	7.26(5.28; 9.24)	6.64(4.72; 8.56)
Rotation			
Range of motion	1.65(1.09; 2.36)	1.81(1.08; 2.85)*	1.67(1.01; 2.35)†

*Mean values with confidence intervals. * indicates a significant result, when comparing with native. † indicates a significant result when compared to Defect. Due to the orientation of the facet joints in the porcine spine, a sigmoid curve is not obtained and it is not possible to calculate neutral zone or neutral zone stiffness, only ROM. Table from study 1 (72).*

4.2. STUDY 2 - CLINICAL TRIAL

4.2.1. PATIENT INCLUSION

Between April 2012 and April 2014, twenty patients were enrolled, and the last follow-up was done in April 2015. In the enrollment period, 179 patients were screened, the flow-diagram below shows the patient flow.

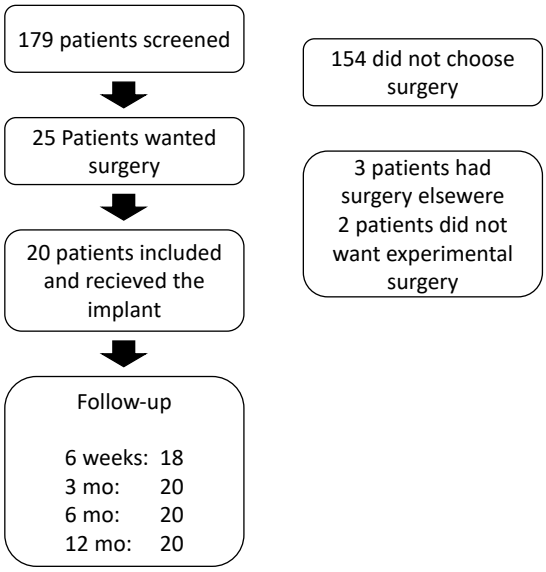


Figure 9. Patient flow. Study 2 (75).

The majority of the patients initially screened, were not ready for surgery. At the outpatient clinic they were informed about the diagnosis and received information about the available treatment options. Despite the offer of surgery within short period of time, usually 2-4 weeks, three patients choose private clinics, accessible through a private health insurance. Two patients were not interested in participating in the trial and were offered standard open discectomy without implant. All twenty patients completed the follow-up, but two patients missed the six-week follow-up visit.

4.2.2. BASELINE DATA

Table 5. Population demographics.

Variable	Distribution
Age	38 ± 9
Sex (female)	50%
Smoking status:	
Current	25%
Past	25%
Never	50%
Work status:	
Working	80%
Disabled from job	10%
Unemployed	5%
In training	5%
Rehabilitation	0%
Sick Leave status:	
Full time	37%
Part time	21%
No	42%
Expect to return to work:	
Already in work	32%
Return to full time	53%
Return to part time	5%
Change job	11%
No	0%
On pension	0%
Sports active:	
Yes, professional	0%
Yes, exercise level	75%
No	25%
Medical history:	
Mental disorder	10%
Musculo skeletal disorder	5%
Nervous disorder	10%
Painkillers:	
Yes, regular	21%
Yes, intermittent	74%
No	5%
Pain medication:	
NSAID and COX inhibitors	65%
Weak analgesics	55%
Opioids and related	50%
Duration of back pain	
No back pain	16%
Less than 3 months	11%
3-12 months	63%
1-2 years	11%
More than 2 years	0%
Duration of leg pain	
No leg pain	0%
Less than 3 months	11%
3-12 months	84%
1-2 years	5%
More than 2 years	0%
Side of surgery	
Left	65%
Right	35%
Level of surgery	
L4-L5	10%
L5-S1	90%

Mean ± SD, or percentage.
Study 2((75).

Baseline data for the 20 patients are seen in table 5. The demographic data corresponds very well with the literature (85), however, in this study, there was a slightly higher representation of L5-S1 herniations. One patient has had sciatica for more than a year, which is noticeably more than the typical patient.

4.2.3. ADVERSE EVENTS

In total four serious adverse events were reported. First subject was a 39-year-old female, with a L5/S1 right side disc herniation, radicular pain, and dysesthesia in her right lateral foot. She enrolled in the trial and received surgery. Initially she reported reduced radiculopathy, but two weeks later she reported mild recurrence of symptoms and one week later she was in severe pain. MR imaging was performed and it was concluded that the patient had a reherniation. The patient was offered a new operation with decompression of the reherniation and instrumented fusion, the latter because of her severe back pain and degenerative findings on the MRI. She chose reoperation and received surgery. At the surgery, the ARO device was removed to allow for instrumentation. At one year follow up, the patient reported continuing back pain and radiculopathy in right leg, although improved. Second subject was a 47-year-old male with known diabetes followed regularly in the endocrinology outpatient clinic because of poor compliance. He developed mild post-operative hyperglycemia and needed additionally insulin, why he was kept in hospital one additional day. Third subject was admitted to hospital with choledocholithiasis and infection 6 months after surgery. She was treated with antibiotics and discharged after 11 days. Last subject developed ileus 9 months after surgery, and was treated conservatively with success.

An additional thirteen adverse events were reported, all minor events not related to the implant, a summary is in appendix. No wound infection, dural tear, or dural hematoma occurred. All serious- and adverse events were judged as not related to the implant. One reoperation was performed, which gives a revision rate of 5% at 1-year follow-up, which is less than previously reported by similar trials (85). It was concluded that the risk and complication rate were not higher in this study with the method including an implant, than compared to standard open discectomy.

4.2.4. OUTCOMES

Patient reported outcome measures are described in Table 6. Back and leg pain mean values from VAS score 0-100, where higher scores indicate more pain. EQ-5D VAS is self-evaluated health on a 0-100 scale, were higher is better health. EQ-5D index is the calculated generic health status that in Denmark ranges from -0.624 – 1, higher scores equal better health status. Since no control group was used, the results were compared to the DaneSpine annual report 2018 (21).

Table 6. PROM compared with DaneSpine.

	Study 2		**DaneSpine**	
	Pre-op	12m	Pre-op	12m
Back Pain	31.8	16.0	45.6	26.2
Leg Pain	55.8	19.7	58.1	24.8
EQ-5D				
VAS	50.6	79.8	46	72
Index	0.39	0.74	0.26	0.71
ODI	37.5	13.9	44.8	20.8
Satisfaction				
Satisfied		88%		
In doubt		6%		
Not satisfied		6%		

DaneSpine – 2018 annual report (21), Study 2 (75).

The mean VAS back and leg pain scores decreased by 15.8 and 36.1 respectively, very similar to DaneSpine, which report a decrease by 19.4 and 33.3, respectively. Oswestry disability score decreased by 23.6, likewise DaneSpine reports a decrease by 24.0. Satisfaction with symptoms was declared by 88% of the patients. DaneSpine do not report this outcome.

4.3. STUDY 3 - SYSTEMATIC REVIEW

4.3.1. LITERATURE SEARCH AND STUDY SELECTION

From the extensive literature search 1477 studies were identified, from which 32 studies met the criteria for inclusion in the systematic review and the subsequent network meta-analysis. Figure 10 illustrates the paper selection process.

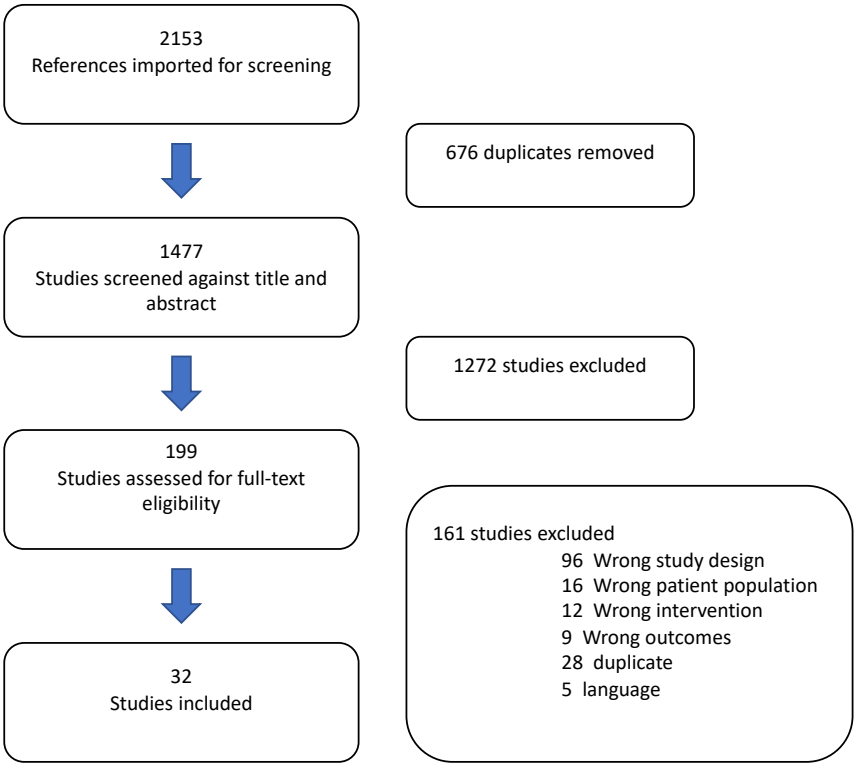


Figure 10. PRISMA flow chart showing the selection process From the manuscript for study 3 (86).

Along with the reasons listed in Figure 10, studies were also excluded if two treatments compared differed only minimal and as a result the intervention and compared treatment were likely to end up in the same treatment group. As an example,

did Ao et al (87), compare two different instruments for endoscopic discectomy. Li et al (88) used a microdiscectomy method with more preservation of the ligamentum flavum, compared to standard partial hemi-laminectomy. Subgroups of lumbar herniations were moreover excluded such as Nie et al (89), only addressing L5-S1 herniations or Thome et al (90), in which only sequestered herniations were included. By applying these restrictions, it is ensured that all investigated treatment methods, could in theory have been used in any of the included study populations, assuring transitivity.

The reviewers' inter-rater reliability in selecting the studies for the review can be seen in Table 7. It shows a high proportional agreement >85% and a moderate kappa. This is in agreement with AMSTAR 2 for critical appraisal of systematic reviews which recommend a minimum of 80% agreement between reviewers (91).

Table 7. Reviewer inter-rater reliability.

Reviewer A Reviewer B	PP SE	KR SE	KR PP
A Yes, B Yes	66	52	6
A Yes, B No	103	33	4
A No, B Yes	22	30	9
A No, B No	643	407	69
Proportionale Agreement	0.85	0.88	0.85
Cohen's Kappa	0.44	0.55	0.40

SE, PP, and KR are the three reviewers.

The 32 RCT studies included are seen in Table 8 (33, 37, 56, 85, 86, 92-119). A total of 4877 participants receiving 8 different treatments were included.

Table 8. Basic demographic data of RCTs included.

Study ID	Country	Surgical intervention	Compara-tor	Sample size	Mean age, years
Abrishamkar 2015	Iran	AUTD	OD	200	40
Anderson 2017	United States	AFrep	TD	80	46
Arts 2009	The Netherland	TD	MD	328	41
Bailey 2013	United States	AFrep	MD	750	42
Bailey 2020	Canada	MD	Cons	128	38
Brouwer 2015	The Netherlands	AUTD	OD	112	43
Chen 2018	China	TD	PEDs	153	40
Cho 2019	Korea	AFrep	OD	60	42
Erginousakis 2011	Greece	AUTD	Cons	62	37
Franke 2009	Germany	TD	MD	100	44
Garg 2011	India	TD	OD	112	38
Gibson 2017	UK	PED	MD	140	41
Gu 2017	China	OD_ds	OD	77	40
Hermantin 1999	United States	PED	OD	60	40
Katayama 2006	Japan	MD	OD	119	38
Krappel 2017	Multicenter EU	OD_ds	OD	146	41
Lee 2015	Korea	AUTD	MD	40	43
Mayer 1993	Germany	PED	MD	40	41
Meyer 2020	Brazil	PED	MD	47	46
Osterman 2006	Finland	MD	Cons	56	38
Peul 2007	The Netherlands	MD	Cons	281	43
Righesso 2007	Brazil	TD	MD	40	44
Ruetten 2008	Germany	PED	MD	178	43
Ryang 2008	Germany	TD	MD	60	39

Teli 2010	Italy	TD	OD	212	40
Thome 2018	Multicenter Europe	AFrep	MD	550	41
Tullberg 1993	Sweden	MD	OD	60	39
Tureyen 2003	Turkey	MD	OD	114	42
Weber 1983	Norway	OD	Cons		
Weinstein 2006	United States	OD	Cons	472	42
Wu 2017	China	OD_ds	OD	100	37
Yu 2017	China	TD	OD	87	61

Cons, conservative treatment; OD, open surgery; MD, microdiscectomy; TD, tubular discectomy; PED, percutaneous endoscopic discectomy; AUTD, percutaneous discectomy; OD_ds, OD and dynamic stabilization; AFrep, annulus repair. Table from manuscript for study 3 (86).

4.3.2. RISK OF BIAS

Blinding of both participants and personnel is not possible in controlled surgical studies, why a high risk of bias is expected in this domain, therefore, this was disregarded in the assessment. But in addition, there were a number of studies with a fairly high risk of bias. Fifteen studies had more than two areas with high risk of bias out of the 13 possible.

To include the risk of bias assessment in the analysis, a stratified analysis was chosen. The analysis was performed for all studies and secondly only for studies with a low risk of bias. The results did not differ significantly, which is why we decided on keeping the high-risk studies in the final analysis, to take advantage of the greater power.

4.3.3. NETWORK META-ANALYSIS

Pairwise meta-analysis showed an overall low heterogeneity and the funnel plots showed a reasonable dispersal without sign of publication bias. Possible effect modifiers were identified as mean age, pain score at baseline, and disability score at baseline. These were compared across the studies in boxplots and by meta-regression as covariates. They were found to have insignificant impact, and no covariates were used in the analysis. Node split analysis was made for treatments with direct comparisons, and showed a general consistency.

Detailed results of the network meta-analysis and discussion of these are presented in the manuscript of study 3 in the appendix. In summary the analysis showed that all the treatments performed at the same level. Although percutaneous discectomy and conservative treatment consistently performed inferior both with regard to statistical and clinical significance. Below are two examples of how we chose to represent the results, a league table with color codes (heatmap) for comparison of treatments and SUCRA for ranking.

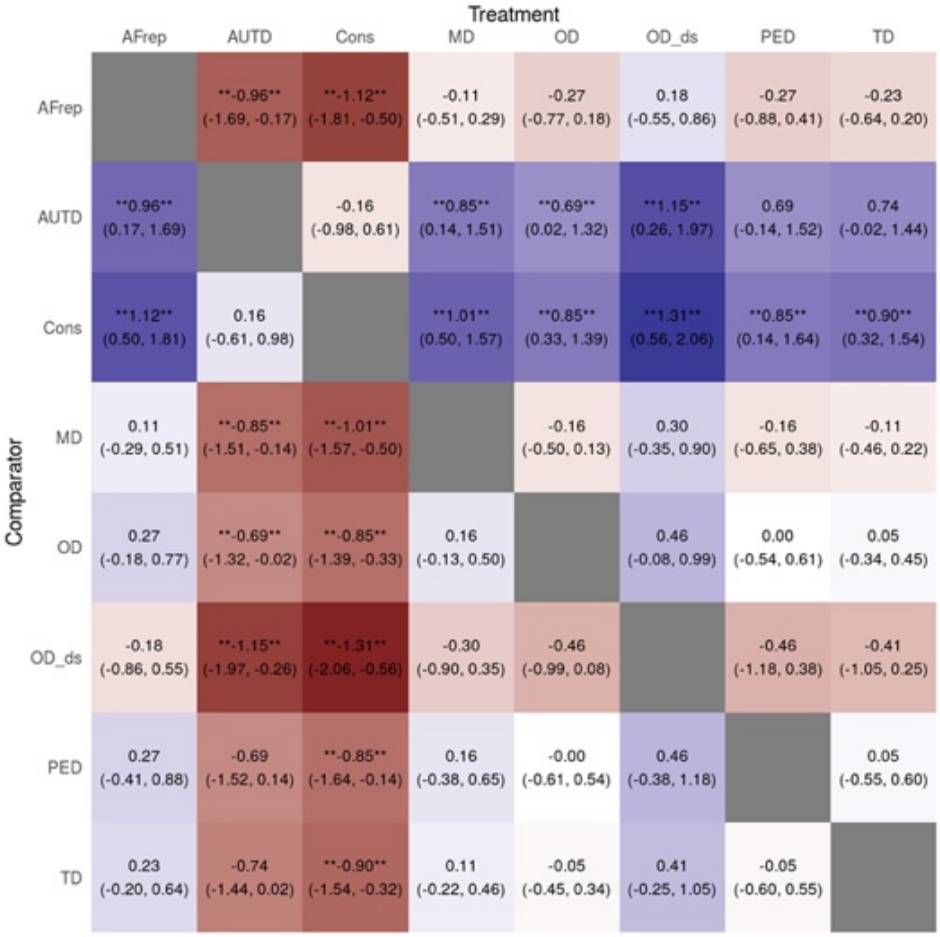


Figure 11. League table show pairwise comparisons for all treatments using the network treatment effect. Color coding highlights treatments effect, with stronger color indicating larger differences. Figure from study 3 (86).

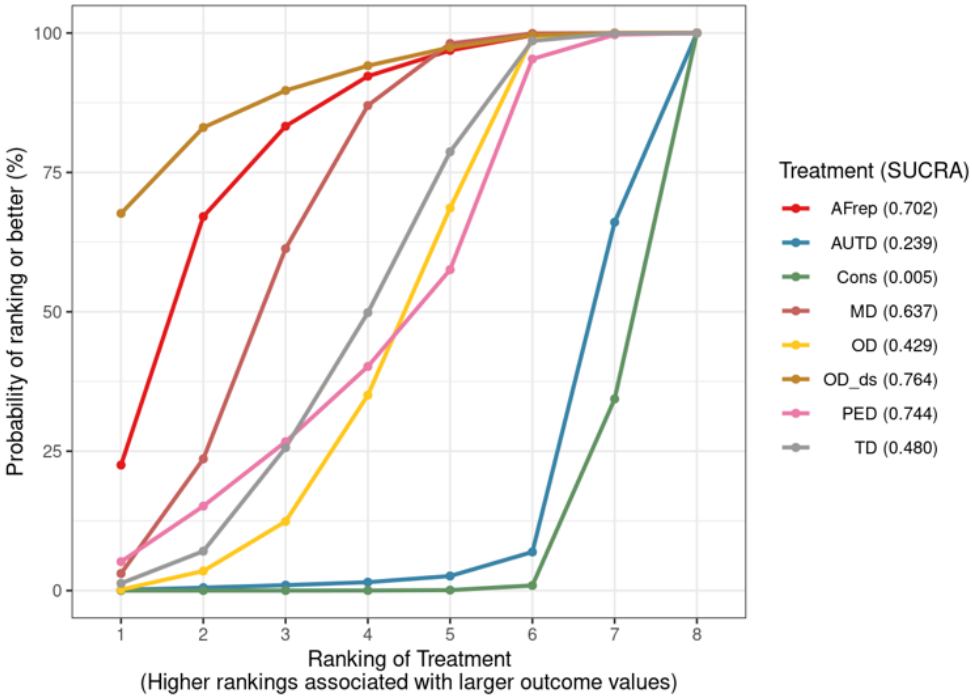


Figure 12. SUCRA values and the graph show the probability of a given treatment to be ranked 1, 2, 3 etc. This is the probability of a certain rank and do not consider the magnitude of difference. Figure from study 3 (86).

CHAPTER 5. DISCUSSION

5.1. STUDY 1- MAIN FINDINGS

Applying a defect in the annulus of a porcine spinal segment gave an increase in ROM, neutral zone, and neutral zone stiffness, indicating increased instability. Repairing the annulus reverted these parameters. Although it was not significant for all outcomes the trend was obvious and global. The experiment was performed ex vivo and only describes the immediate effect of the repair. Therefore, one cannot directly transfer the results to the clinical setting. However, it can be deduced that a large defect in annulus affects the biomechanics. It was expected since studies investigating lesions to the annulus have shown this previously (120, 121). Whether the repair of annulus brings the movement pattern back to native state, or just increases the resilience, is not easily assessed. It is likely that the integrity of the disc will suffer permanent damage. Nevertheless, the repair provided an immediate increase in stability. If the long-term impact is to be investigated, in vivo tests must be performed.

The plug was not able to hold the nucleus. Not because the plug was expelled, but because nucleus could leak out through the pores of the plug. Nucleus changes through life from being very viscous in young individuals to becoming more fibrotic with age (7). Removed disc herniations are often described as rubbery in texture. The animals used for the experiment were younger than 5 months. It is possible that nucleus would not have leaked out in the same way, had we used a model that more closely simulated the clinical conditions. On the basis of the missing ability to contain nucleus together with the difficulties in using soft anchors, that needs drilling for fixation in a narrow space, we decided not to proceed with the method.

5.1.1. ADVANTAGES OF IN VIVO BIOMECHANICAL TEST

If spinal biomechanical tests are to be performed, the most common set-up is cadaver testing in a biomechanical laboratory. It is often not possible to make in vivo studies of biomechanical conditions, as it mostly requires very invasive procedures to make these measurements. However, there are examples of in vivo human testing, such as when Wilke et al measured the pressure in the intervertebral disc during various activities (122). In this case, it was the authors themselves who were the test subjects and today it would probably be difficult to get permission for such an experiment.

Using an animal cadaver instead of human is always a compromise, but there are some advantages. First of all, the costs and availability. Furthermore, using animals in experiments gives a high degree of homogeneity and thus low variance. In an ideal laboratory set-up, the only varying factor is the intervention. A number of different animals have been used in spinal research, most common large animal models are pig,

sheep, dog, and goat (123). Since these are quadrupeds not bipeds like humans, the question of difference in anatomy and biomechanical characteristic has been raised. The porcine anatomy is very similar with small differences, most notable in the cervical spine, whereas the lumbar spine is very comparable and perhaps the best animal model (124). One important difference from humans is the medulla, that extents all the way to L6 in pigs. This detail together with a slightly smaller spinal canal makes it difficult to perform posterior surgery, why most surgery is done anterior. Despite the horizontal position of the spine, quadrupeds experience the same axial pressure on the intervertebral disc as humans (125), and biomechanical behavior is very similar, especially the porcine lumbar spine (126).

5.1.2. LIMITATIONS

The biggest limitation of the animal model used, is the lacking ability to simulate the disease. Animal models of intervertebral disc degeneration have been developed. By applying an injury to the disc, it is possible to start the process of degeneration (127). However, a lumbar disc herniation disease model has not been established. Moreover, the in vitro study in the laboratory only provides a limited momentary simulation of the condition. Therefore, there will be a lack of information about what prolonged exposure does to the motion segment, and the forces acting on the motion segment are different in vivo from in vitro (128). Finally, it is not possible to investigate how the cell and tissue response to the repair unfolds. In vitro experiments are therefore best suited for a rough sorting of suitable designs which subsequently should be tested in vivo.

5.1.3. CLINICAL USAGE

Annulus repair is still very new and experimental. The methods investigated and researched are very different. Still, one can divide them into two main groups.

There are methods intended to work purely mechanically, which purpose are to close the defect in annulus in a durable way. Some of the first attempts to close the defect mechanically were made with sutures. However, both in vivo and ex vivo studies concluded that the sutures were not able to contain the nucleus, not even when combined with tissue glue (129, 130). There is a commercially available instrument for suturing annulus, Xclose Tissue Repair System (Anulex Technologies, Minnetonka, MN). A RCT including 750 patients found no difference in revision rate for patients where annulus was sutured using Xclose, compared to patients receiving only discectomy (104). A different concept is to plug the defect. Bron et al used a polyethylene plug with barbs on, together with nucleus replacement in an ovine model (131). They found promising results with ex vivo biomechanical testing, but a subsequent in vivo study showed displacement of the plugs and endplate destruction. The only commercially available implant for annulus repair that uses the plugging method, to my knowledge, is Barricaide (Intrinsic Therapeutics, Woburn,MA). This

implant was tested in a RCT including 554 patients and showed a significant decreased revision rate when used in combination with discectomy for large annular defects compared to standard discectomy (94). However, it could be criticized that Intrinsic Therapeutics who produce the implant also sponsored the study. Furthermore, clustering and treatment variation may limit the evidence from this trial, since the trial was carried out on 21 centers during 4 years.

A different approach to annulus repair focuses on bio-integration and seeks to facilitate healing of annulus fibrosus and even often aims at regenerating the nucleus pulposus, (reverting the disc degeneration). Suggested methods are plentiful and often includes biomolecular treatment (132, 133), stem cells (134-136), and advanced bio-scaffolds (137), although some of these are more aimed at the disc degeneration. Majority of these methods are only experimental and not ready for in clinical trials.

5.2. STUDY 2 – CLINICAL TRIAL

5.2.1. MAIN FINDINGS

This study confirmed what was expected, that the new implant did not pose an increased risk to patients. In part, because it is used outside the spinal canal and thus not in contact with the more sensitive structures such as the dural sack and nerve roots. In addition, it is used in a surgery of short duration with few complications and with mostly healthy patients. None of the observed adverse events could be attributed to the implant. A single patient underwent a revision with fusion. This gives a revision rate of 5% at 1-year follow-up equal to similar studies and reports (70, 85).

5.2.2. STRENGTHS

The study's primary purpose was to ensure that the implant used did not impose side effects or increased risk. The high quality and very strict adherence to all guidelines is emphasized by the use of appropriate guidelines such as Good Clinical Practice (GCP), COHORT, registration at Clinicaltrials.org, and the use of an external Clinical Research Organization. Implants for surgical use do not have to be approved by the Danish Medicines Agency in the same way as medicaments. It is different in the United States where FDA approval is required before an implant can enter the market. Therefore, FDA approval is often used as a hallmark of quality in the European market, but it is not a requirement. From a quality assurance perspective, however, patients with new implants should at least be closely monitored to observe any side effects.

5.2.3. LIMITATIONS

One of the limitations in the study was the inclusion time. It took about 2 years to include the 20 patients in the trial. With this low inclusion rate, clustering of patients and variation in treatment is a risk. Out of 179 screened patients only 25 patients had the need and desire for surgery. The main reason being that the patients declined surgery and chose conservative therapy.

As there was no control group, it is not possible to compare directly with discectomy only. Instead, results might be compared with other similar studies. There will of course be a risk that the populations are not the same or that the treatments vary with regard to factors other than the one that is to be examined (the implant in this case). These potential biases have been eliminated in RCT studies, which is why they rank high in the evidence-based hierarchy. However, it is possible to get an impression of whether the groups are similar by comparing the demographic data for the populations. Inclusion and exclusion criteria can also provide an indication of whether the groups can be compared. DaneSpine reported in 2018 (21) that the average age of lumbar disc herniation operated patients was 47 years, this is considerably older than

study 2 where the average age was 38 years. This can probably be explained by the age limit set in study 2 (18-55 years). Study 2 had additional exclusion criteria that would not exclude patients in a normal clinical setup like DaneSpine: previous lumbar surgery, osteoporosis, multiple herniations, and several others, see section 3.2.1. There is also a significant difference in the pre-operative function score, ODI. Where DanesSpine has a starting point of 45, it is 38 for study 2. However, there is roughly the same gender distribution, and the pre-operative leg pains are also comparable, 58 and 56, respectively. A large RCT which is frequently referred to, SPORT (36) is more alike study 2 in population. Age and gender distribution is roughly the same, as well as the inclusion and exclusion criteria. But, both the DaneSpine patients and the patients in the SPORT study have a higher ODI score, which indicates that these patients have more severe symptoms before surgery. Scores for the three populations are seen in Figure 13. The differences in the before mentioned conditions, especially pre-operative ODI, make it difficult to compare directly.

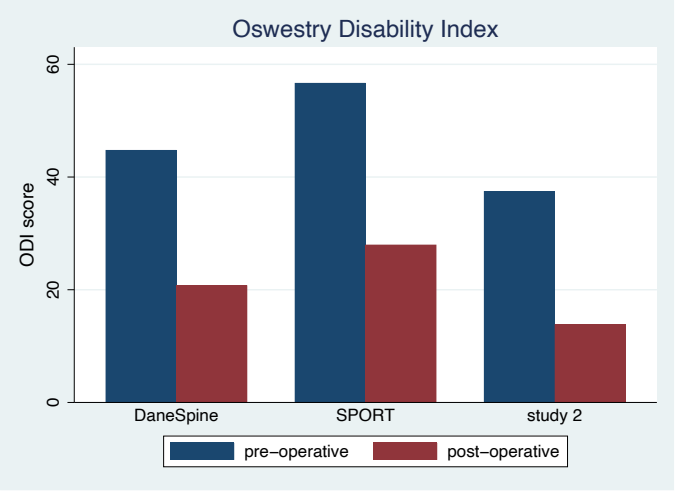


Figure 13. This illustrates the different starting point in ODI score for the three studies and why a direct comparison is not recommended.

The expectation for the new implant was that it could improve the back pain. But the same limitation applies as mentioned for the function score. Back pain was assessed as a patient reported outcome measure (VAS scale). It has previously been shown that the VAS score can be quite unreliable, especially at the individual level and when comparing different groups; it is best used to follow the same group over time (138).

5.3. STUDY 3 – SYSTEMATIC REVIEW

5.3.1. MAIN FINDINGS

Most of the treatment modalities in the systematic review performed equally well. However, conservative treatment and percutaneous discectomy performed inferior than average; dynamic stabilization better than average.

Looking at the conservative treatment in the network, there were 6 studies included in this treatment group. Peul et al (37), a medium size RCT found no difference in VAS and ODI scores after 1 year. Weinstein et al (85), as well as Osterman et al. (113), found a small non-significant benefit in surgery. The two studies that showed the greatest benefit were Bailey et al (56) and Erginousakis et al (106), the latter comparing with percutaneous discectomy, which actually performed poorly in the overall analysis. Weber et al (33) did not report reoperation rate, VAS, or ODI score. Although surgery turned out better than conservative treatment, there are circumstances that make it likely, that the true effect is not revealed. Most significant is the large cross-over. This applies to both Weinstein, Peul, Bailey, and Osterman with up to 55% cross-over. Despite attempts to eliminate the effect of cross-over through statistics, it profoundly affects the outcome. The problem is that cross-over offsets the difference. Presumably, the patients who have benefited most from the opposite treatment switch over. Thus, it may happen that a patient randomized to conservative treatment crosses over as he or she has too much pain to continue conservative treatment. Conversely, a patient randomized to surgery will switch if he or she has a decrease in pain and surgery cannot be justified because of this. Since cross-over seems to be unavoidable, well designed observational studies might be a better solution when comparing surgery and conservative treatment (139).

The objective of Percutaneous discectomy is to remove nucleus pulposus from inside the disc, with the purpose to relieve the pressure, and presumably remove the herniation. This is significantly different from the other treatment modalities which all target the herniation directly, and seeks to preserve nucleus. Three studies compared the effectiveness of percutaneous discectomy with standard discectomy with and without a microscope (101-103). These studies were very similar (chi-squared test showed a $I^2 = 0{,}00\%$) and the trend consistently showed inferior results of percutaneous discectomy. In the study by Brouwer et al, it was necessary to reoperate 26 patients with standard discectomy, out of 57 patients who initially received percutaneous discectomy. A previous review has made the same conclusion (31).

Discectomy with dynamic stabilization performed better than average in relieving pain and improving functional score. The three studies in this group used different

methods to induce stabilization (96-98). Krappel et al investigated the DIAM spinal stabilization system (Medtronic Sofamor Danek, Memphis, Tennessee, USA). They found a small improvement but insignificant. There is to my knowledge no other controlled trials investigating the use of DIAM in herniation patients, but, a study with a mixed cohort of patients with lumbar disc herniation and spinal stenosis found an increased reoperation rate with the use of the DIAM implant (140). Gu et al examined the effect of Wallis interspinous device (Zimmerbiomet) and found a remarkable difference in VAS score. Although it was smaller than what is required to generate a Minimal Clinical Important Difference (MCID), it is the reason why the dynamic stability group performs better than the other treatment groups. Wallis has been studied mostly as a replacement for PLIF. Reports of the use in lumbar disc herniation patients are few, but a recent retrospective controlled trial found no difference (141). The situation is very much the same for Wu et al, who used unilateral internal fixation and found a significant difference in the ODI score. Previous results with internal fixation is in contrast to this (142). Therefore, the results pointing to an advantage for dynamic stabilization must be interpreted with caution, as only a few trials have compared the combination of surgery and dynamic stabilization to standard discectomy for lumbar disc herniation, and these point in different directions.

Worth mentioning in the context of this dissertation is the annulus repair. The primary purpose of annulus repair was to avoid reherniation and thereby reoperation. Four studies were included in the annulus repair group (93, 94, 100, 104). Similar to the dynamic stabilization group, the methods for annulus repair differs substantially. In the study of Andersson et al, a cryopreserved amniotic membrane (cAM) was left in the annulus defect to augment healing. The cAM was chosen as it is known to have anti-inflammatory effect (143). Although the cAM group outperformed the control group, the study sample is too small to impact the result. A large 600 patient RCT was conducted by Bailey et al, who investigated the commercially available Xclose Tissue Repair System (Anulex Technologies, Minnetonka, MN). This system is used to suture the annulus defect, much like the well-known meniscus suture system. The reoperation rate was similar in the two groups, demonstrating no benefit from Xclose. The studies of Thome et al and Cho et al both investigated Barricaid (Intrinsic Therapeutics), unfortunately Cho et al did not report reoperation rates. Thome et al conducted a large 550 patients RCT and found that the Barricaid group had only half the reoperations of the control group. However, this does not impact the network meta-analysis as the reoperation rate corresponds to the average in other groups. This probably indicates that it was the control group that performed worse than the average. Overall, annulus repair did not improve the reoperation rate.

5.3.2. LITTERATURE SEARCH AND PICO

Initially, the review question was formulated as: how do lumbar disc herniation patients treated with annulus repair perform compared to standard discectomy? After thorough discussion and screening of the literature, we chose to examine all current

surgical treatments with the option of performing a NMA if possible. We chose the contemporary surgical treatments, since this is of interest for surgeons. Should you implement a new technique? If you do not have equipment or a suitable set-up, what alternatives are there then? It could have been an advantage to include all known treatments, both obsolete and non-surgical. Confer section 3.3.4, more connections in the network provide greater precision, as there will be a greater basis for comparison. So even though the treatments are not of interest, they could enhance the network meta-analysis. Of course, only studies with the same type of population may be included to comply with the assumption of transitivity. It could be argued, conversely, that older treatment methods should not be included. There is a constant progress in technology and equipment. Open discectomy has probably not changed drastically, but within endoscopy there have been significant changes, and the optics in 1993 cannot be compared with today's equipment (144).

Follow-up of interest was decided to be at one year. This is because we valued the outcome reoperation highly. We did not use a two-year follow-up, which is commonly used for measuring reoperations, because we also wanted to see an effect of the operation, which is presumably greatest early. It is of course possible to investigate several follow-up timepoints, but some limitation is needed. The extremely early outcomes CRP, operation time, hospitalization time and more, had no interest in this review.

5.3.3. DATA EXTRACTION AND QUALITY ASSESMENT

The final decision on which outcomes to include was made after the literature search. Characterization on reherniation is very diverse, often lacking, or with a great uncertainty (59). Revision surgery, which can be a consequence of reherniation, is a very objective measure, reported by the majority of studies. Likewise, details about infection are often missing as well. A superficial infection can be treated with antibiotics, while a deep infection frequently needs to be revised. If the complication requires revision, it can be argued that the complication is serious. The patient must again be exposed to the risks posed by surgery, and the result of revision is often inferior to primary surgery. With these arguments, we found that reoperation was a meaningful proxy for complications, why we chose this outcome in the review. For patient reported outcome measures we chose pain on a visual analog scale and functional score, either Roland Morris or Oswestry Disability Index.

Different tools for assessing risk of bias in a systematic review exists (145). For this review the Cochrane Neck and Back Review Group recommended tool for assessing risk was used (79). The quality assessment showed considerable many studies with a high risk of bias (ROB). Fifteen studies had more than two areas with high risk of bias out of the 13 possible. This gives an impression of poor study design, in many cases, lack of information about the details. No exact cut-off point is set for how many high

ROB is allowed before exclusion. The quality assessment is included in the overall assessment and in the CINeMA evaluation (83).

5.3.4. NETWORK META-ANALYSIS

One of the challenges with the network meta-analysis is communicating the result. The NMA is still a fairly new tool and there are no guidelines yet on how to report the results, yet (146). Since there are many dimensions to consider, one cannot depict “one final result” in a graph. Often a table is used which shows "summary of findings". This can become an unmanageable size and the overview is lost when there are more than 3-4 treatments and at the same time different outcomes (147). Instead, one can convey the results in a few different ways, thus giving an impression of the results. There are different options: forest-plot, rank-plot, ranking heatmap, radar plot and more. We chose a heatmap with paired network comparisons with the opportunity to discover patterns in the results. In addition, surface under the cumulative ranking (SUCRA) curve method, as it is easy to interpret visually. It is inevitable that some information is not shown. We have not divided results into direct, indirect and network comparisons. It is also not clear what quality the results are, or the level of evidence, but this was taken into account in the CINeMA assessment. Also, reminding that there are many different outcomes after surgery, we have selected three that we think are important, but for other professionals, other outcomes may be more important.

CHAPTER 6. CONCLUSION

The purpose of the PhD thesis was to test and investigate new methods of treating lumbar disc herniation, this has been achieved. Two new implants have been tested. The first was an experimental way to repair the annulus. The biomechanical impact on the intervertebral disc after insertion was promising, but the ability to retain nucleus pulposus was lacking. The second implant was examined in a clinical study. This was designed to provide temporary axial rotational stabilization. Primary focus was on safety which was on a par with standard discectomy. The effect could not be measured, an RCT is needed to measure this. Finally, a systematic review of current surgical treatments was conducted. The results showed that conservative treatment as well as percutaneous discectomy are inferior to the other treatments. This applies to patients who have persistent radicular pain after 6 weeks due to disc herniation. Dynamic stabilization and annulus repair performed best. However, this must be taken with certain reservations as the methods are very different and very few clinical studies have yet been performed. There are no studies yet that have shown convincing effect of annulus repair.

CHAPTER 7. FUTURE PERSPECTIVES

In view of the results of the manuscript included in this PhD dissertation as well as previous systematic reviews in accordance with this, percutaneous discectomy should not be used for treatment of lumbar disc herniation. It has also been confirmed that surgery is better at relieving pain and improving function in lumbar disc herniation than conservative treatment after 6 weeks of persistent pain.

There is a constant progress in regenerative medicine. Although much knowledge has been gained about cartilage regeneration through research, there is still much not understood. However, the progress that has been made gives rise to the expectation that at some point we may facilitate cartilage regeneration. Probably primarily for younger individuals who have had an early cartilage injury with the following intervertebral disc degeneration or lumbar disc herniation.

The large variation in results from different clinical trials should be examined. There seem to be factors other than the surgical technique that are crucial to the outcome. It could be at the treatment level, such as the surgeon or hospital setup; or at the patient level. One of the factors that varied the most was duration of symptoms. Optimal time for surgery has already gained some focus. Future research should further investigate the optimal time for surgery and possible cut-off points for duration of symptoms.

As previous argued, large RCTs are costly, difficult to perform and often unprecise because of cross-over. National databases with open access for research purpose should be utilized instead. In order to identify other factors suspectable for impacting the outcome, an accurate registration of procedures and PROMs is essential.

REFERENCES

1. Laseque C. Consideration sur la sciatique. Arch Gen Med II 1864;7:558-80.
2. Forst J. Contribution a l'etude clinique de la sciatique. Paris1881.
3. Kraemer J. Intervertebral disk disease. 3rd ed: Thieme; 2009.
4. Benneker LM, Heini PF, Alini M, Anderson SE, Ito K. 2004 Young Investigator Award Winner: vertebral endplate marrow contact channel occlusions and intervertebral disc degeneration. Spine (Phila Pa 1976). 2005;30(2):167-73. Epub 2005/01/13. doi: 10.1097/01.brs.0000150833.93248.09. PubMed PMID: 15644751.
5. Antoniou J, Steffen T, Nelson F, Winterbottom N, Hollander AP, Poole RA, et al. The human lumbar intervertebral disc: evidence for changes in the biosynthesis and denaturation of the extracellular matrix with growth, maturation, ageing, and degeneration. The Journal of clinical investigation. 1996;98(4):996-1003. Epub 1996/08/15. doi: 10.1172/JCI118884. PubMed PMID: 8770872; PubMed Central PMCID: PMCPMC507515.
6. Urban JP, Smith S, Fairbank JC. Nutrition of the intervertebral disc. Spine (Phila Pa 1976). 2004;29(23):2700-9. Epub 2004/11/27. doi: 10.1097/01.brs.0000146499.97948.52. PubMed PMID: 15564919.
7. Boos N, Weissbach S, Rohrbach H, Weiler C, Spratt KF, Nerlich AG. Classification of age-related changes in lumbar intervertebral discs: 2002 Volvo Award in basic science. Spine (Phila Pa 1976). 2002;27(23):2631-44. Epub 2002/12/04. doi: 10.1097/00007632-200212010-00002. PubMed PMID: 12461389.
8. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine (Phila Pa 1976). 2006;31(18):2151-61. Epub 2006/08/18. doi: 10.1097/01.brs.0000231761.73859.2c. PubMed PMID: 16915105.
9. Thompson JP, Pearce RH, Schechter MT, Adams ME, Tsang IK, Bishop PB. Preliminary evaluation of a scheme for grading the gross morphology of the human intervertebral disc. Spine (Phila Pa 1976). 1990;15(5):411-5. Epub 1990/05/01. doi: 10.1097/00007632-199005000-00012. PubMed PMID: 2363069.
10. Olmarker K, Rydevik B, Holm S, Bagge U. Effects of experimental graded compression on blood flow in spinal nerve roots. A vital microscopic study on the porcine cauda equina. J Orthop Res. 1989;7(6):817-23. Epub 1989/01/01. doi: 10.1002/jor.1100070607. PubMed PMID: 2795321.
11. Kawakami M, Weinstein JN, Chatani K, Spratt KF, Meller ST, Gebhart GF. Experimental lumbar radiculopathy. Behavioral and histologic changes in a model of radicular pain after spinal nerve root irritation with chromic gut ligatures in the rat. Spine (Phila Pa 1976). 1994;19(16):1795-802. Epub 1994/08/15. doi: 10.1097/00007632-199408150-00002. PubMed PMID: 7973977.
12. Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P. Pathophysiology of disk-related sciatica. I.--Evidence supporting a chemical

component. Joint, bone, spine : revue du rhumatisme. 2006;73(2):151-8. Epub 2005/07/28. doi: 10.1016/j.jbspin.2005.03.003. PubMed PMID: 16046173.
13. Olmarker K, Rydevik B, Nordborg C. Autologous nucleus pulposus induces neurophysiologic and histologic changes in porcine cauda equina nerve roots. Spine (Phila Pa 1976). 1993;18(11):1425-32. Epub 1993/09/01. PubMed PMID: 8235812.
14. Garcia-Cosamalon J, del Valle ME, Calavia MG, Garcia-Suarez O, Lopez-Muniz A, Otero J, et al. Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain? J Anat. 2010;217(1):1-15. Epub 2010/05/12. doi: 10.1111/j.1469-7580.2010.01227.x. PubMed PMID: 20456524; PubMed Central PMCID: PMCPMC2913007.
15. Bush K, Cowan N, Katz DE, Gishen P. The natural history of sciatica associated with disc pathology. A prospective study with clinical and independent radiologic follow-up. Spine (Phila Pa 1976). 1992;17(10):1205-12. Epub 1992/10/01. doi: 10.1097/00007632-199210000-00013. PubMed PMID: 1440010.
16. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am. 1990;72(3):403-8. Epub 1990/03/01. PubMed PMID: 2312537.
17. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. The New England journal of medicine. 1994;331(2):69-73. Epub 1994/07/14. doi: 10.1056/NEJM199407143310201. PubMed PMID: 8208267.
18. Fardon DF, Milette PC, Combined Task Forces of the North American Spine Society ASoSR, American Society of N. Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine (Phila Pa 1976). 2001;26(5):E93-E113. Epub 2001/03/10. doi: 10.1097/00007632-200103010-00006. PubMed PMID: 11242399.
19. Fardon DF, Williams AL, Dohring EJ, Murtagh FR, Gabriel Rothman SL, Sze GK. Lumbar disc nomenclature: version 2.0: Recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology. The spine journal : official journal of the North American Spine Society. 2014;14(11):2525-45. Epub 2014/04/29. doi: 10.1016/j.spinee.2014.04.022. PubMed PMID: 24768732.
20. Heliövaara M. Epidemiology of sciatica and herniated lumbar intervertebral disc: The Social Insurance Institution, Research Institute for Social Security; 1988.
21. Andersen M. Årsrapport DaneSpine 2018 2018 [cited 2020 June]. Available from: http://drks.ortopaedi.dk/wp-content/uploads/2019/12/Årsrapport-DaneSpine-2018.pdf.

22. Sundhedsstyrelsen, Authority TDH. National clinical guideline for the non-surgical treatment of recent onset lumbar nerve root compression (lumbar radiculopathy). 2016.
23. Katz JN. Lumbar disc disorders and low-back pain: socioeconomic factors and consequences. J Bone Joint Surg Am. 2006;88 Suppl 2(SUPPL. 2):21-4. Epub 2006/04/06. doi: 10.2106/JBJS.E.01273. PubMed PMID: 16595438.
24. Battié MC, Videman T, Levälahti E, Gill K, Kaprio J. Genetic and environmental effects on disc degeneration by phenotype and spinal level: a multivariate twin study. Spine (Phila Pa 1976). 2008;33(25):2801-8. Epub 2008/12/04. doi: 10.1097/BRS.0b013e31818043b7. PubMed PMID: 19050586.
25. Sørensen IG, Jacobsen P, Gyntelberg F, Suadicani P. Occupational and other predictors of herniated lumbar disc disease-a 33-year follow-up in the Copenhagen male study. Spine (Phila Pa 1976). 2011;36(19):1541-6. Epub 2011/01/29. doi: 10.1097/BRS.0b013e3181f9b8d4. PubMed PMID: 21270695.
26. Sundhedsstyrelsen. National klinisk retningslinje for ikke-kirurgisk behandling af nylig opstået lumbal ner- verodspåvirkning (lumbal radikulopati). 2016.
27. Vroomen PC, de Krom MC, Wilmink JT, Kester AD, Knottnerus JA. Lack of effectiveness of bed rest for sciatica. The New England journal of medicine. 1999;340(6):418-23. Epub 1999/02/11. doi: 10.1056/nejm199902113400602. PubMed PMID: 9971865.
28. Hofstee DJ, Gijtenbeek JM, Hoogland PH, van Houwelingen HC, Kloet A, Lötters F, et al. Westeinde sciatica trial: randomized controlled study of bed rest and physiotherapy for acute sciatica. Journal of neurosurgery. 2002;96(1 Suppl):45-9. Epub 2002/01/19. doi: 10.3171/spi.2002.96.1.0045. PubMed PMID: 11797655.
29. Chou R, Hashimoto R, Friedly J, Fu R, Bougatsos C, Dana T, et al. Epidural Corticosteroid Injections for Radiculopathy and Spinal Stenosis: A Systematic Review and Meta-analysis. Ann Intern Med. 2015;163(5):373-81. Epub 2015/08/25. doi: 10.7326/m15-0934. PubMed PMID: 26302454.
30. Pinto RZ, Maher CG, Ferreira ML, Ferreira PH, Hancock M, Oliveira VC, et al. Drugs for relief of pain in patients with sciatica: systematic review and meta-analysis. BMJ. 2012;344:e497. doi: 10.1136/bmj.e497.
31. Lewis RA, Williams NH, Sutton AJ, Burton K, Din NU, Matar HE, et al. Comparative clinical effectiveness of management strategies for sciatica: systematic review and network meta-analyses. The spine journal : official journal of the North American Spine Society. 2015;15(6):1461-77. Epub 2014/01/15. doi: 10.1016/j.spinee.2013.08.049. PubMed PMID: 24412033.
32. Tay EC, Chacha PB. Midline prolapse of a lumbar intervertebral disc with compression of the cauda equina. J Bone Joint Surg Br. 1979;61(1):43-6. Epub 1979/02/01. doi: 10.1302/0301-620X.61B1.154521. PubMed PMID: 154521.
33. Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. Spine (Phila Pa 1976). 1983;8(2):131-40. Epub 1983/03/01. PubMed PMID: 6857385.

34. Atlas SJ, Deyo RA, Keller RB, Chapin AM, Patrick DL, Long JM, et al. The Maine Lumbar Spine Study, Part II. 1-year outcomes of surgical and nonsurgical management of sciatica. Spine (Phila Pa 1976). 1996;21(15):1777-86. Epub 1996/08/01. doi: 10.1097/00007632-199608010-00011. PubMed PMID: 8855462.
35. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long-term outcomes of surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: 10 year results from the maine lumbar spine study. Spine (Phila Pa 1976). 2005;30(8):927-35. Epub 2005/04/19. doi: 10.1097/01.brs.0000158954.68522.2a. PubMed PMID: 15834338.
36. Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA. 2006;296(20):2451-9. Epub 2006/11/23. doi: 10.1001/jama.296.20.2451. PubMed PMID: 17119141; PubMed Central PMCID: PMCPMC2562254.
37. Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, et al. Surgery versus prolonged conservative treatment for sciatica. The New England journal of medicine. 2007;356(22):2245-56. Epub 2007/06/01. doi: 10.1056/NEJMoa064039. PubMed PMID: 17538084.
38. van den Hout WB, Peul WC, Koes BW, Brand R, Kievit J, Thomeer RT, et al. Prolonged conservative care versus early surgery in patients with sciatica from lumbar disc herniation: cost utility analysis alongside a randomised controlled trial. BMJ. 2008;336(7657):1351-4. Epub 2008/05/27. doi: 10.1136/bmj.39583.709074.BE. PubMed PMID: 18502912; PubMed Central PMCID: PMCPMC2427123.
39. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse. Cochrane Database Syst Rev. 2007(2):CD001350. Epub 2007/04/20. doi: 10.1002/14651858.CD001350.pub4. PubMed PMID: 17443505; PubMed Central PMCID: PMCPMC7028003.
40. Rasouli MR, Rahimi-Movaghar V, Shokraneh F, Moradi-Lakeh M, Chou R. Minimally invasive discectomy versus microdiscectomy/open discectomy for symptomatic lumbar disc herniation. Cochrane Database Syst Rev. 2014(9):CD010328. Epub 2014/09/04. doi: 10.1002/14651858.CD010328.pub2. PubMed PMID: 25184502.
41. Smith MM, Foley KT. Micro endoscopic Discectomy (MED): The First 100 Cases. Neurosurgery. 1998;43(3):701-. doi: 10.1097/00006123-199809000-00303.
42. Kamper SJ, Ostelo RW, Rubinstein SM, Nellensteijn JM, Peul WC, Arts MP, et al. Minimally invasive surgery for lumbar disc herniation: a systematic review and meta-analysis. Eur Spine J. 2014;23(5):1021-43. Epub 2014/01/21. doi: 10.1007/s00586-013-3161-2. PubMed PMID: 24442183.
43. Wiltse LL, Spencer CW. New uses and refinements of the paraspinal approach to the lumbar spine. Spine (Phila Pa 1976). 1988;13(6):696-706. Epub 1988/06/01. PubMed PMID: 3175760.

44. Kambin P, Sampson S. Posterolateral percutaneous suction-excision of herniated lumbar intervertebral discs. Report of interim results. Clin Orthop Relat Res. 1986(207):37-43. Epub 1986/06/01. PubMed PMID: 3720102.
45. Rothman RH, Simeone FA, Herkowitz HN. Rothman-Simeone and Herkowitz's, the spine2018.
46. Onik G, Helms CA, Ginsburg L, Hoaglund FT, Morris J. Percutaneous lumbar diskectomy using a new aspiration probe. American Journal of Roentgenology. 1985;144(6):1137-40. doi: 10.2214/ajr.144.6.1137.
47. Shapiro S. Long-term follow up of 57 patients undergoing automated percutaneous discectomy. Journal of neurosurgery. 1995;83(1):31-3. Epub 1995/07/01. doi: 10.3171/jns.1995.83.1.0031. PubMed PMID: 7782846.
48. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse: updated Cochrane Review. Spine (Phila Pa 1976). 2007;32(16):1735-47. Epub 2007/07/17. doi: 10.1097/BRS.0b013e3180bc2431. PubMed PMID: 17632394.
49. Williams NH, Lewis R, Din NU, Matar HE, Fitzsimmons D, Phillips CJ, et al. A systematic review and meta-analysis of biological treatments targeting tumour necrosis factor alpha for sciatica. Eur Spine J. 2013;22(9):1921-35. Epub 2013/03/27. doi: 10.1007/s00586-013-2739-z. PubMed PMID: 23529742; PubMed Central PMCID: PMCPMC3777072.
50. Miyamoto K. [Long-term follow-up results of anterior discectomy and interbody fusion for lumbar disc herniation]. Nihon Seikeigeka Gakkai Zasshi. 1991;65(12):1179-90. Epub 1991/12/01. PubMed PMID: 1787342.
51. Putzier M, Schneider SV, Funk JF, Tohtz SW, Perka C. The surgical treatment of the lumbar disc prolapse: nucleotomy with additional transpedicular dynamic stabilization versus nucleotomy alone. Spine (Phila Pa 1976). 2005;30(5):E109-14. Epub 2005/03/02. doi: 10.1097/01.brs.0000154630.79887.ef. PubMed PMID: 15738772.
52. McGirt MJ, Ambrossi GL, Datoo G, Sciubba DM, Witham TF, Wolinsky JP, et al. Recurrent disc herniation and long-term back pain after primary lumbar discectomy: review of outcomes reported for limited versus aggressive disc removal. Neurosurgery. 2009;64(2):338-44; discussion 44-5. Epub 2009/02/05. doi: 10.1227/01.NEU.0000337574.58662.E2. PubMed PMID: 19190461.
53. Sloan SR, Jr., Lintz M, Hussain I, Hartl R, Bonassar LJ. Biologic Annulus Fibrosus Repair: A Review of Preclinical In Vivo Investigations. Tissue Eng Part B Rev. 2018;24(3):179-90. Epub 2017/11/07. doi: 10.1089/ten.TEB.2017.0351. PubMed PMID: 29105592.
54. Klassen PD, Bernstein DT, Köhler HP, Arts MP, Weiner B, Miller LE, et al. Bone-anchored annular closure following lumbar discectomy reduces risk of complications and reoperations within 90 days of discharge. J Pain Res. 2017;10:2047-55. Epub 2017/09/13. doi: 10.2147/jpr.S144500. PubMed PMID: 28894388; PubMed Central PMCID: PMCPMC5584895.
55. Schoenfeld AJ, Bono CM. Does surgical timing influence functional recovery after lumbar discectomy? A systematic review. Clin Orthop Relat Res.

2015;473(6):1963-70. Epub 2014/02/15. doi: 10.1007/s11999-014-3505-1. PubMed PMID: 24526298; PubMed Central PMCID: PMCPMC4419004.
56. Bailey CS, Rasoulinejad P, Taylor D, Sequeira K, Miller T, Watson J, et al. Surgery versus Conservative Care for Persistent Sciatica Lasting 4 to 12 Months. The New England journal of medicine. 2020;382(12):1093-102. Epub 2020/03/19. doi: 10.1056/NEJMoa1912658. PubMed PMID: 32187469.
57. Fisher C, Noonan V, Bishop P, Boyd M, Fairholm D, Wing P, et al. Outcome evaluation of the operative management of lumbar disc herniation causing sciatica. Journal of neurosurgery. 2004;100(4 Suppl Spine):317-24. Epub 2004/04/09. doi: 10.3171/spi.2004.100.4.0317. PubMed PMID: 15070138.
58. Carragee EJ, Han MY, Suen PW, Kim D. Clinical outcomes after lumbar discectomy for sciatica: the effects of fragment type and anular competence. J Bone Joint Surg Am. 2003;85(1):102-8. Epub 2003/01/21. PubMed PMID: 12533579.
59. Miller LE, McGirt MJ, Garfin SR, Bono CM. Association of Annular Defect Width After Lumbar Discectomy With Risk of Symptom Recurrence and Reoperation: Systematic Review and Meta-analysis of Comparative Studies. Spine (Phila Pa 1976). 2018;43(5):E308-E15. Epub 2017/11/28. doi: 10.1097/BRS.0000000000002501. PubMed PMID: 29176471; PubMed Central PMCID: PMCPMC5815639.
60. Pearson AM, Blood EA, Frymoyer JW, Herkowitz H, Abdu WA, Woodward R, et al. SPORT lumbar intervertebral disk herniation and back pain: does treatment, location, or morphology matter? Spine (Phila Pa 1976). 2008;33(4):428-35. Epub 2008/02/19. doi: 10.1097/BRS.0b013e31816469de. PubMed PMID: 18277876; PubMed Central PMCID: PMCPMC2785121.
61. Andersen MO, Ernst C, Rasmussen J, Dahl S, Carreon LY. Return to work after lumbar disc surgery is related to the length of preoperative sick leave. Dan Med J. 2017;64(7). Epub 2017/07/05. PubMed PMID: 28673379.
62. Spengler DM, Ouellette EA, Battié M, Zeh J. Elective discectomy for herniation of a lumbar disc. Additional experience with an objective method. J Bone Joint Surg Am. 1990;72(2):230-7. Epub 1990/02/01. PubMed PMID: 2303509.
63. Sørensen LV, Mors O, Skovlund O. A prospective study of the importance of psychological and social factors for the outcome after surgery in patients with slipped lumbar disk operated upon for the first time. Acta Neurochir (Wien). 1987;88(3-4):119-25. Epub 1987/01/01. doi: 10.1007/bf01404148. PubMed PMID: 3687498.
64. Shriver MF, Xie JJ, Tye EY, Rosenbaum BP, Kshettry VR, Benzel EC, et al. Lumbar microdiscectomy complication rates: a systematic review and meta-analysis. Neurosurgical focus. 2015;39(4):E6. Epub 2015/10/02. doi: 10.3171/2015.7.Focus15281. PubMed PMID: 26424346.
65. McGirt MJ, Eustacchio S, Varga P, Vilendecic M, Trummer M, Gorensek M, et al. A prospective cohort study of close interval computed tomography and magnetic resonance imaging after primary lumbar discectomy: factors associated with recurrent disc herniation and disc height loss. Spine (Phila Pa 1976).

2009;34(19):2044-51. Epub 2009/09/05. doi: 10.1097/BRS.0b013e3181b34a9a. PubMed PMID: 19730212.
66. Ambrossi GL, McGirt MJ, Sciubba DM, Witham TF, Wolinsky JP, Gokaslan ZL, et al. Recurrent lumbar disc herniation after single-level lumbar discectomy: incidence and health care cost analysis. Neurosurgery. 2009;65(3):574-8; discussion 8. Epub 2009/08/19. doi: 10.1227/01.NEU.0000350224.36213.F9. PubMed PMID: 19687703.
67. Carragee EJ, Spinnickie AO, Alamin TF, Paragioudakis S. A prospective controlled study of limited versus subtotal posterior discectomy: short-term outcomes in patients with herniated lumbar intervertebral discs and large posterior anular defect. Spine (Phila Pa 1976). 2006;31(6):653-7. Epub 2006/03/17. doi: 10.1097/01.brs.0000203714.76250.68. PubMed PMID: 16540869.
68. Kim KT, Lee DH, Cho DC, Sung JK, Kim YB. Preoperative Risk Factors for Recurrent Lumbar Disk Herniation in L5-S1. Journal of spinal disorders & techniques. 2015;28(10):E571-7. Epub 2014/08/05. doi: 10.1097/bsd.0000000000000041. PubMed PMID: 25089673.
69. Leven D, Passias PG, Errico TJ, Lafage V, Bianco K, Lee A, et al. Risk Factors for Reoperation in Patients Treated Surgically for Intervertebral Disc Herniation: A Subanalysis of Eight-Year SPORT Data. J Bone Joint Surg Am. 2015;97(16):1316-25. Epub 2015/08/21. doi: 10.2106/jbjs.N.01287. PubMed PMID: 26290082; PubMed Central PMCID: PMCPMC5480260.
70. Martin BI, Mirza SK, Flum DR, Wickizer TM, Heagerty PJ, Lenkoski AF, et al. Repeat surgery after lumbar decompression for herniated disc: the quality implications of hospital and surgeon variation. The spine journal : official journal of the North American Spine Society. 2012;12(2):89-97. Epub 2011/12/24. doi: 10.1016/j.spinee.2011.11.010. PubMed PMID: 22193055; PubMed Central PMCID: PMCPMC3299929.
71. Chen M, Le DQ, Hein S, Li P, Nygaard JV, Kassem M, et al. Fabrication and characterization of a rapid prototyped tissue engineering scaffold with embedded multicomponent matrix for controlled drug release. Int J Nanomedicine. 2012;7:4285-97. Epub 2012/08/21. doi: 10.2147/IJN.S33083. PubMed PMID: 22904634; PubMed Central PMCID: PMCPMC3418070.
72. Rickers K, Bendtsen M, Le DQS, Veen AJ, Bunger CE. Biomechanical evaluation of annulus fibrosus repair with scaffold and soft anchors in an ex vivo porcine model. SICOT J. 2018;4(2426-8887 (Print)):38. Epub 2018/09/08. doi: 10.1051/sicotj/2018020. PubMed PMID: 30192225; PubMed Central PMCID: PMCPMC6128169.
73. Smit TH, van Tunen MS, van der Veen AJ, Kingma I, van Dieen JH. Quantifying intervertebral disc mechanics: a new definition of the neutral zone. BMC musculoskeletal disorders. 2011;12:38. Epub 2011/02/09. doi: 10.1186/1471-2474-12-38. PubMed PMID: 21299900; PubMed Central PMCID: PMCPMC3041726.
74. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.

Lancet. 2007;370(9596):1453-7. Epub 2007/12/08. doi: 10.1016/S0140-6736(07)61602-X. PubMed PMID: 18064739.
75. Rickers KW, Li H, Robie B, Bunger C. Temporary axial rotation stabilization for lumbar disc herniation surgery with the ARO((R)) spinal system: a prospective analysis of safety and clinical efficacy. Journal of spine surgery (Hong Kong). 2019;5(1):124-31. Epub 2019/04/30. doi: 10.21037/jss.2018.12.13. PubMed PMID: 31032447; PubMed Central PMCID: PMCPMC6465462.
76. Schmidt H, Kettler A, Heuer F, Simon U, Claes L, Wilke HJ. Intradiscal pressure, shear strain, and fiber strain in the intervertebral disc under combined loading. Spine (Phila Pa 1976). 2007;32(7):748-55. Epub 2007/04/07. doi: 10.1097/01.brs.0000259059.90430.c2. PubMed PMID: 17414908.
77. Warburton A, Girdler SJ, Mikhail CM, Ahn A, Cho SK. Biomaterials in Spinal Implants: A Review. Neurospine. 2020;17(1):101-10. Epub 2019/11/07. doi: 10.14245/ns.1938296.148. PubMed PMID: 31694360; PubMed Central PMCID: PMCPMC7136103.
78. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-84. Epub 2015/06/02. doi: 10.7326/M14-2385. PubMed PMID: 26030634.
79. Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, et al. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. Spine (Phila Pa 1976). 2015;40(21):1660-73. Epub 2015/07/25. doi: 10.1097/BRS.0000000000001061. PubMed PMID: 26208232.
80. van Valkenhoef G, Lu G, de Brock B, Hillege H, Ades AE, Welton NJ. Automating network meta-analysis. Res Synth Methods. 2012;3(4):285-99. Epub 2012/12/01. doi: 10.1002/jrsm.1054. PubMed PMID: 26053422.
81. van Valkenhoef G, Dias S, Ades AE, Welton NJ. Automated generation of node-splitting models for assessment of inconsistency in network meta-analysis. Res Synth Methods. 2016;7(1):80-93. Epub 2015/10/16. doi: 10.1002/jrsm.1167. PubMed PMID: 26461181; PubMed Central PMCID: PMCPMC5057346.
82. Beliveau A, Boyne DJ, Slater J, Brenner D, Arora P. BUGSnet: an R package to facilitate the conduct and reporting of Bayesian network Meta-analyses. BMC Med Res Methodol. 2019;19(1):196. Epub 2019/10/24. doi: 10.1186/s12874-019-0829-2. PubMed PMID: 31640567; PubMed Central PMCID: PMCPMC6805536.
83. Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. PLoS Med. 2020;17(4):e1003082. Epub 2020/04/04. doi: 10.1371/journal.pmed.1003082. PubMed PMID: 32243458; PubMed Central PMCID: PMCPMC7122720 following competing interests: ME is a member of the Editorial Board of PLOS Medicine.

84. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6. doi: 10.1136/bmj.39489.470347.AD.
85. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. JAMA. 2006;296(20):2441-50. Epub 2006/11/23. doi: 10.1001/jama.296.20.2441. PubMed PMID: 17119140; PubMed Central PMCID: PMCPMC2553805.
86. Rickers KW, Pedersen PH, Tvedebrink T, Eiskjaer SP. Comparison of interventions for lumbar disc herniation: a systematic review with network meta-analysis. The spine journal : official journal of the North American Spine Society. 2021. Epub 2021/03/06. doi: 10.1016/j.spinee.2021.02.022. PubMed PMID: 33667683.
87. Ao S, Wu J, Zheng W, Zhou Y. A Novel Targeted Foraminoplasty Device Improves the Efficacy and Safety of Foraminoplasty in Percutaneous Endoscopic Lumbar Discectomy: Preliminary Clinical Application of 70 Cases. World Neurosurg. 2018;115:e263-e71. Epub 2018/04/17. doi: 10.1016/j.wneu.2018.04.032. PubMed PMID: 29660553.
88. Li T, Han D, Liu B, Zhang X, Wang P, Qiu Y. Clinical assessment of reformed lumbar microdiscectomy. Eur J Orthop Surg Traumatol. 2014;24(1):23-7. Epub 2013/02/16. doi: 10.1007/s00590-012-1123-8. PubMed PMID: 23412248.
89. Nie H, Zeng J, Song Y, Chen G, Wang X, Li Z, et al. Percutaneous Endoscopic Lumbar Discectomy for L5-S1 Disc Herniation Via an Interlaminar Approach Versus a Transforaminal Approach: A Prospective Randomized Controlled Study With 2-Year Follow Up. Spine (Phila Pa 1976). 2016;41 Suppl 19:B30-b7. Epub 2016/07/28. doi: 10.1097/brs.0000000000001810. PubMed PMID: 27454540.
90. Thome C, Barth M, Scharf J, Schmiedek P. Outcome after lumbar sequestrectomy compared with microdiscectomy: a prospective randomized study. J Neurosurg Spine. 2005;2(3):271-8. Epub 2005/03/31. doi: 10.3171/spi.2005.2.3.0271. PubMed PMID: 15796351.
91. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008. Epub 2017/09/25. doi: 10.1136/bmj.j4008. PubMed PMID: 28935701; PubMed Central PMCID: PMCPMC5833365 at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.
92. Meyer G, ID DAR, Cristante AF, Marcon RM, Coutinho TP, Torelli AG, et al. Percutaneous Endoscopic Lumbar Discectomy Versus Microdiscectomy for the Treatment of Lumbar Disc Herniation: Pain, Disability, and Complication Rate-A Randomized Clinical Trial. Int J Spine Surg. 2020;14(1):72-8. Epub 2020/03/05. doi:

10.14444/7010. PubMed PMID: 32128306; PubMed Central PMCID: PMCPMC7043817.
93. Cho PG, Shin DA, Park SH, Ji GY. Efficacy of a Novel Annular Closure Device after Lumbar Discectomy in Korean Patients : A 24-Month Follow-Up of a Randomized Controlled Trial. J Korean Neurosurg Soc. 2019;62(6):691-9. Epub 2019/11/05. doi: 10.3340/jkns.2019.0071. PubMed PMID: 31679318; PubMed Central PMCID: PMCPMC6835150.
94. Thome C, Klassen PD, Bouma GJ, Kursumovic A, Fandino J, Barth M, et al. Annular closure in lumbar microdiscectomy for prevention of reherniation: a randomized clinical trial. The spine journal : official journal of the North American Spine Society. 2018;18(12):2278-87. Epub 2018/05/08. doi: 10.1016/j.spinee.2018.05.003. PubMed PMID: 29730458.
95. Chen Z, Zhang L, Dong J, Xie P, Liu B, Wang Q, et al. Percutaneous transforaminal endoscopic discectomy compared with microendoscopic discectomy for lumbar disc herniation: 1-year results of an ongoing randomized controlled trial. J Neurosurg Spine. 2018;28(3):300-10. Epub 2018/01/06. doi: 10.3171/2017.7.SPINE161434. PubMed PMID: 29303469.
96. Wu HR, Wang HW, Xu WK, Wu ZY. The short-term effects of discectomy combined with unilateral non-fusion internal fixation for the treatment of lumbar disc herniation. Int J Clin Exp Med. 2017;10(6):9448-55. PubMed PMID: WOS:000404534900092.
97. Krappel F, Brayda-Bruno M, Alessi G, Remacle JM, Lopez LA, Fernandez JJ, et al. Herniectomy versus herniectomy with the DIAM spinal stabilization system in patients with sciatica and concomitant low back pain: results of a prospective randomized controlled multicenter trial. Eur Spine J. 2017;26(3):865-76. Epub 2016/10/06. doi: 10.1007/s00586-016-4796-6. PubMed PMID: 27704286.
98. Gu H, Chang Y, Zeng S, Gao Y, Zhan S, Zheng Q. Efficacy of the Wallis interspinous implant for primary lumbar disc herniation : a prospective randomised controlled trial. Acta Orthop Belg. 2017;83(3):405-15. Epub 2017/09/01. PubMed PMID: 30423641.
99. Gibson JNA, Subramanian AS, Scott CEH. A randomised controlled trial of transforaminal endoscopic discectomy vs microdiscectomy. Eur Spine J. 2017;26(3):847-56. Epub 2016/11/26. doi: 10.1007/s00586-016-4885-6. PubMed PMID: 27885470.
100. Anderson DG, Popov V, Raines AL, O'Connell J. Cryopreserved Amniotic Membrane Improves Clinical Outcomes Following Microdiscectomy. Clinical spine surgery. 2017;30(9):413-8. Epub 2017/05/31. doi: 10.1097/BSD.0000000000000544. PubMed PMID: 28557902.
101. Lee SH, Bae JS. Comparison of clinical and radiological outcomes after automated open lumbar discectomy and conventional microdiscectomy: a prospective randomized trial. Int J Clin Exp Med. 2015;8(8):12135-48. Epub 2015/11/10. PubMed PMID: 26550124; PubMed Central PMCID: PMCPMC4612809.

102. Brouwer PA, Brand R, van den Akker-van Marle ME, Jacobs WC, Schenk B, van den Berg-Huijsmans AA, et al. Percutaneous laser disc decompression versus conventional microdiscectomy in sciatica: a randomized controlled trial. The spine journal : official journal of the North American Spine Society. 2015;15(5):857-65. Epub 2015/01/24. doi: 10.1016/j.spinee.2015.01.020. PubMed PMID: 25614151.
103. Abrishamkar S, Kouchakzadeh M, Mirhosseini A, Tabesh H, Rezvani M, Moayednia A, et al. Comparison of open surgical discectomy versus plasma-laser nucleoplasty in patients with single lumbar disc herniation. J Res Med Sci. 2015;20(12):1133-7. Epub 2016/03/10. doi: 10.4103/1735-1995.172979. PubMed PMID: 26958046; PubMed Central PMCID: PMCPMC4766818.
104. Bailey A, Araghi A, Blumenthal S, Huffmon GV, Anular Repair Clinical Study G. Prospective, multicenter, randomized, controlled study of anular repair in lumbar discectomy: two-year follow-up. Spine (Phila Pa 1976). 2013;38(14):1161-9. Epub 2013/02/09. doi: 10.1097/BRS.0b013e31828b2e2f. PubMed PMID: 23392414.
105. Garg B, Nagraja UB, Jayaswal A. Microendoscopic versus open discectomy for lumbar disc herniation: a prospective randomised study. J Orthop Surg (Hong Kong). 2011;19(1):30-4. Epub 2011/04/27. doi: 10.1177/230949901101900107. PubMed PMID: 21519072.
106. Erginousakis D, Filippiadis DK, Malagari A, Kostakos A, Brountzos E, Kelekis NL, et al. Comparative prospective randomized study comparing conservative treatment and percutaneous disk decompression for treatment of intervertebral disk herniation. Radiology. 2011;260(2):487-93. Epub 2011/05/27. doi: 10.1148/radiol.11101094. PubMed PMID: 21613439.
107. Teli M, Lovi A, Brayda-Bruno M, Zagra A, Corriero A, Giudici F, et al. Higher risk of dural tears and recurrent herniation with lumbar micro-endoscopic discectomy. Eur Spine J. 2010;19(3):443-50. Epub 2010/02/04. doi: 10.1007/s00586-010-1290-4. PubMed PMID: 20127495; PubMed Central PMCID: PMCPMC2899770.
108. Franke J, Greiner-Perth R, Boehm H, Mahlfeld K, Grasshoff H, Allam Y, et al. Comparison of a minimally invasive procedure versus standard microscopic discotomy: a prospective randomised controlled clinical trial. Eur Spine J. 2009;18(7):992-1000. Epub 2009/04/11. doi: 10.1007/s00586-009-0964-2. PubMed PMID: 19360440; PubMed Central PMCID: PMCPMC2899586.
109. Arts MP, Brand R, van den Akker ME, Koes BW, Bartels RH, Peul WC, et al. Tubular diskectomy vs conventional microdiskectomy for sciatica: a randomized controlled trial. JAMA. 2009;302(2):149-58. Epub 2009/07/09. doi: 10.1001/jama.2009.972. PubMed PMID: 19584344.
110. Ryang YM, Oertel MF, Mayfrank L, Gilsbach JM, Rohde V. Standard open microdiscectomy versus minimal access trocar microdiscectomy: results of a prospective randomized study. Neurosurgery. 2008;62(1):174-81; discussion 81-2. Epub 2008/02/28. doi: 10.1227/01.NEU.0000311075.56486.C5. PubMed PMID: 18300905.

111. Ruetten S, Komp M, Merk H, Godolias G. Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: a prospective, randomized, controlled study. Spine (Phila Pa 1976). 2008;33(9):931-9. Epub 2008/04/23. doi: 10.1097/BRS.0b013e31816c8af7. PubMed PMID: 18427312.
112. Righesso O, Falavigna A, Avanzi O. Comparison of open discectomy with microendoscopic discectomy in lumbar disc herniations: results of a randomized controlled trial. Neurosurgery. 2007;61(3):545-9; discussion 9. Epub 2007/09/21. doi: 10.1227/01.NEU.0000290901.00320.F5. PubMed PMID: 17881967.
113. Osterman H, Seitsalo S, Karppinen J, Malmivaara A. Effectiveness of microdiscectomy for lumbar disc herniation: a randomized controlled trial with 2 years of follow-up. Spine (Phila Pa 1976). 2006;31(21):2409-14. Epub 2006/10/07. doi: 10.1097/01.brs.0000239178.08796.52. PubMed PMID: 17023847.
114. Katayama Y, Matsuyama Y, Yoshihara H, Sakai Y, Nakamura H, Nakashima S, et al. Comparison of surgical outcomes between macro discectomy and micro discectomy for lumbar disc herniation: a prospective randomized study with surgery performed by the same spine surgeon. Journal of spinal disorders & techniques. 2006;19(5):344-7. Epub 2006/07/11. doi: 10.1097/01.bsd.0000211201.93125.1c. PubMed PMID: 16826006.
115. Tureyen K. One-level one-sided lumbar disc surgery with and without microscopic assistance: 1-year outcome in 114 consecutive patients. Journal of neurosurgery. 2003;99(3 Suppl):247-50. Epub 2003/10/18. doi: 10.3171/spi.2003.99.3.0247. PubMed PMID: 14563140.
116. Hermantin FU, Peters T, Quartararo L, Kambin P. A prospective, randomized study comparing the results of open discectomy with those of video-assisted arthroscopic microdiscectomy. J Bone Joint Surg Am. 1999;81(7):958-65. Epub 1999/07/31. doi: 10.2106/00004623-199907000-00008. PubMed PMID: 10428127.
117. Tullberg T, Isacson J, Weidenhielm L. Does microscopic removal of lumbar disc herniation lead to better results than the standard procedure? Results of a one-year randomized study. Spine (Phila Pa 1976). 1993;18(1):24-7. Epub 1993/01/01. doi: 10.1097/00007632-199301000-00005. PubMed PMID: 8434321.
118. Mayer HM, Brock M. Percutaneous endoscopic discectomy: surgical technique and preliminary results compared to microsurgical discectomy. Journal of neurosurgery. 1993;78(2):216-25. Epub 1993/02/01. doi: 10.3171/jns.1993.78.2.0216. PubMed PMID: 8267686.
119. Yu D, Wang G, Wei Y, Yin G. The effect of posterior microendoscopy discectomy and open surgery on lumbar disc herniation. Biomedical Research (India). 2017;28(20):8874-7.
120. Michalek AJ, Iatridis JC. Height and torsional stiffness are most sensitive to annular injury in large animal intervertebral discs. The spine journal : official journal of the North American Spine Society. 2012;12(5):425-32. Epub 2012/05/26. doi: 10.1016/j.spinee.2012.04.001. PubMed PMID: 22627276; PubMed Central PMCID: PMCPMC3376192.

121. Thompson RE, Pearcy MJ, Downing KJ, Manthey BA, Parkinson IH, Fazzalari NL. Disc lesions and the mechanics of the intervertebral joint complex. Spine (Phila Pa 1976). 2000;25(23):3026-35. Epub 2001/01/06. doi: 10.1097/00007632-200012010-00010. PubMed PMID: 11145814.
122. Wilke HJ, Neef P, Caimi M, Hoogland T, Claes LE. New in vivo measurements of pressures in the intervertebral disc in daily life. Spine (Phila Pa 1976). 1999;24(8):755-62. Epub 1999/05/01. doi: 10.1097/00007632-199904150-00005. PubMed PMID: 10222525.
123. Alini M, Eisenstein SM, Ito K, Little C, Kettler AA, Masuda K, et al. Are animal models useful for studying human disc disorders/degeneration? Eur Spine J. 2008;17(1):2-19. Epub 2007/07/17. doi: 10.1007/s00586-007-0414-y. PubMed PMID: 17632738; PubMed Central PMCID: PMCPMC2365516.
124. Busscher I, Ploegmakers JJ, Verkerke GJ, Veldhuizen AG. Comparative anatomical dimensions of the complete human and porcine spine. Eur Spine J. 2010;19(7):1104-14. Epub 2010/02/27. doi: 10.1007/s00586-010-1326-9. PubMed PMID: 20186441; PubMed Central PMCID: PMCPMC2900026.
125. Smit TH. The use of a quadruped as an in vivo model for the study of the spine - biomechanical considerations. Eur Spine J. 2002;11(2):137-44. Epub 2002/04/17. doi: 10.1007/s005860100346. PubMed PMID: 11956920; PubMed Central PMCID: PMCPMC3610505.
126. Wilke HJ, Geppert J, Kienle A. Biomechanical in vitro evaluation of the complete porcine spine in comparison with data of the human spine. Eur Spine J. 2011;20(11):1859-68. Epub 2011/06/16. doi: 10.1007/s00586-011-1822-6. PubMed PMID: 21674213; PubMed Central PMCID: PMCPMC3207338.
127. Omlor GW, Nerlich AG, Wilke HJ, Pfeiffer M, Lorenz H, Schaaf-Keim M, et al. A new porcine in vivo animal model of disc degeneration: response of anulus fibrosus cells, chondrocyte-like nucleus pulposus cells, and notochordal nucleus pulposus cells to partial nucleotomy. Spine (Phila Pa 1976). 2009;34(25):2730-9. Epub 2009/11/27. doi: 10.1097/BRS.0b013e3181b723c9. PubMed PMID: 19940730.
128. Wilke HJ, Claes L, Schmitt H, Wolf S. A universal spine tester for in vitro experiments with muscle force simulation. Eur Spine J. 1994;3(2):91-7. Epub 1994/01/01. doi: 10.1007/BF02221446. PubMed PMID: 7874556.
129. Heuer F, Ulrich S, Claes L, Wilke HJ. Biomechanical evaluation of conventional anulus fibrosus closure methods required for nucleus replacement. Laboratory investigation. J Neurosurg Spine. 2008;9(3):307-13. Epub 2008/10/22. doi: 10.3171/SPI/2008/9/9/307. PubMed PMID: 18928230.
130. Ahlgren BD, Lui W, Herkowitz HN, Panjabi MM, Guiboux JP. Effect of anular repair on the healing strength of the intervertebral disc: a sheep model. Spine (Phila Pa 1976). 2000;25(17):2165-70. Epub 2000/09/06. doi: 10.1097/00007632-200009010-00004. PubMed PMID: 10973397.
131. Bron JL, van der Veen AJ, Helder MN, van Royen BJ, Smit TH, Skeletal Tissue Engineering Group A, et al. Biomechanical and in vivo evaluation of experimental closure devices of the annulus fibrosus designed for a goat nucleus

replacement model. Eur Spine J. 2010;19(8):1347-55. Epub 2010/04/20. doi: 10.1007/s00586-010-1384-z. PubMed PMID: 20401620; PubMed Central PMCID: PMCPMC2989188.
132. Masuda K, Imai Y, Okuma M, Muehleman C, Nakagawa K, Akeda K, et al. Osteogenic protein-1 injection into a degenerated disc induces the restoration of disc height and structural changes in the rabbit anular puncture model. Spine (Phila Pa 1976). 2006;31(7):742-54. Epub 2006/04/04. doi: 10.1097/01.brs.0000206358.66412.7b. PubMed PMID: 16582847.
133. Walsh AJ, Bradford DS, Lotz JC. In vivo growth factor treatment of degenerated intervertebral discs. Spine (Phila Pa 1976). 2004;29(2):156-63. Epub 2004/01/15. doi: 10.1097/01.Brs.0000107231.67854.9f. PubMed PMID: 14722406.
134. Freeman BJC, Kuliwaba JS, Jones CF, Shu CC, Colloca CJ, Zarrinkalam MR, et al. Allogeneic Mesenchymal Precursor Cells Promote Healing in Postero-lateral Annular Lesions and Improve Indices of Lumbar Intervertebral Disc Degeneration in an Ovine Model. Spine (Phila Pa 1976). 2016;41(17):1331-9. Epub 2016/02/26. doi: 10.1097/BRS.0000000000001528. PubMed PMID: 26913464.
135. Acosta FL, Jr., Metz L, Adkisson HD, Liu J, Carruthers-Liebenberg E, Milliman C, et al. Porcine intervertebral disc repair using allogeneic juvenile articular chondrocytes or mesenchymal stem cells. Tissue Eng Part A. 2011;17(23-24):3045-55. Epub 2011/09/14. doi: 10.1089/ten.tea.2011.0229. PubMed PMID: 21910592; PubMed Central PMCID: PMCPMC3226053.
136. Henriksson HB, Svanvik T, Jonsson M, Hagman M, Horn M, Lindahl A, et al. Transplantation of human mesenchymal stems cells into intervertebral discs in a xenogeneic porcine model. Spine (Phila Pa 1976). 2009;34(2):141-8. Epub 2008/12/30. doi: 10.1097/BRS.0b013e31818f8c20. PubMed PMID: 19112334.
137. Hegewald AA, Medved F, Feng D, Tsagogiorgas C, Beierfuss A, Schindler GA, et al. Enhancing tissue repair in annulus fibrosus defects of the intervertebral disc: analysis of a bio-integrative annulus implant in an in-vivo ovine model. J Tissue Eng Regen Med. 2015;9(4):405-14. Epub 2013/11/15. doi: 10.1002/term.1831. PubMed PMID: 24227682.
138. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798-804. Epub 2005/07/08. doi: 10.1111/j.1365-2702.2005.01121.x. PubMed PMID: 16000093.
139. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. The New England journal of medicine. 2000;342(25):1878-86. Epub 2000/06/22. doi: 10.1056/nejm200006223422506. PubMed PMID: 10861324.
140. Sur YJ, Kong CG, Park JB. Survivorship analysis of 150 consecutive patients with DIAM™ implantation for surgery of lumbar spinal stenosis and disc herniation. Eur Spine J. 2011;20(2):280-8. Epub 2010/10/19. doi: 10.1007/s00586-010-1599-z. PubMed PMID: 20953966; PubMed Central PMCID: PMCPMC3030713.
141. Zhou Z, Jin X, Wang C, Wang L. Wallis interspinous device versus discectomy for lumbar disc herniation : A comparative study. Orthopade.

2019;48(2):165-9. Epub 2018/10/13. doi: 10.1007/s00132-018-3639-z. PubMed PMID: 30310936.
142. White AH, von Rogov P, Zucherman J, Heiden D. Lumbar laminectomy for herniated disc: a prospective controlled comparison with internal fixation fusion. Spine (Phila Pa 1976). 1987;12(3):305-7. Epub 1987/04/01. doi: 10.1097/00007632-198704000-00021. PubMed PMID: 3296238.
143. Tseng SC. HC-HA/PTX3 Purified From Amniotic Membrane as Novel Regenerative Matrix: Insight Into Relationship Between Inflammation and Regeneration. Invest Ophthalmol Vis Sci. 2016;57(5):ORSFh1-8. Epub 2016/04/27. doi: 10.1167/iovs.15-17637. PubMed PMID: 27116665; PubMed Central PMCID: PMCPMC4855828.
144. Mayer HM, Brock M. Percutaneous endoscopic lumbar discectomy (PELD). Neurosurg Rev. 1993;16(2):115-20. Epub 1993/01/01. doi: 10.1007/BF00258242. PubMed PMID: 8345904.
145. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. Epub 2019/08/30. doi: 10.1136/bmj.l4898. PubMed PMID: 31462531.
146. Bafeta A, Trinquart L, Seror R, Ravaud P. Reporting of results from network meta-analyses: methodological systematic review. Bmj. 2014;348:g1741. Epub 2014/03/13. doi: 10.1136/bmj.g1741. PubMed PMID: 24618053; PubMed Central PMCID: PMCPMC3949412 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
147. Mbuagbaw L, Rochwerg B, Jaeschke R, Heels-Andsell D, Alhazzani W, Thabane L, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. Syst Rev. 2017;6(1):79. Epub 2017/04/14. doi: 10.1186/s13643-017-0473-z. PubMed PMID: 28403893; PubMed Central PMCID: PMCPMC5389085.

APPENDIX

Appendix A. Search String

Search strategy from the literature search in study 3.

PubMed

Search ((((((("Controlled Clinical Trial"[Publication Type] OR "Controlled Clinical Trials as Topic"[Mesh])) OR (((random*[Text Word] OR controlled[Text Word] OR crossover[Text Word] OR cross-over[Text Word] OR blind*[Text Word] OR mask*[Text Word])) AND (trial[Text Word] OR trials[Text Word] OR study[Text Word] OR studies[Text Word] OR analys*[Text Word] OR analyz*[Text Word]))) OR rct[Text Word]) OR (((singl*[Text Word] OR doubl*[Text Word] OR tripl*[Text Word])) AND (blind[Text Word] OR mask[Text Word]))) OR placebo[Text Word]))) AND ((((((((((((((((((("Intervertebral Disc Displacement"[Mesh]) OR ((disc displacement*[Text Word] OR disk displacement*[Text Word]))) OR ((disc prolaps*[Text Word] OR disk prolaps*[Text Word]))) OR ((prolapsed disc*[Text Word] OR prolapsed disk*[Text Word]))) OR ((disc hernia*[Text Word] OR disk hernia*[Text Word]))) OR ((herniated intervertebral disc*[Text Word] OR herniated intervertebral disk*[Text Word]))) OR (((herniated disc*[Text Word] OR herniated disk*[Text Word])))) OR (((prolapsed intervertebral disc*[Text Word] OR prolapsed intervertebral disk*[Text Word])))) OR ((slipped disc*[Text Word] OR slipped disk*[Text Word]))) OR (((slipped intervertebral disc*[Text Word] OR slipped intervertebral disk*[Text Word])))))) AND ((((((((((("Diskectomy"[Mesh]) OR ((diskectom*[Text Word] OR discectom*[Text Word]))) OR (((micro-diskectom*[Text Word] OR micro-discectom*[Text Word])))) OR ((annulus closure device*[Text Word] OR annular closure device*[Text Word]))) OR ((annulus device*[Text Word] OR annular device*[Text Word]))) OR ((annulus repair*[Text Word] OR annular repair*[Text Word]))) OR barricaid[Text Word]) OR xclose[Text Word]) OR dynesys[Text Word]) OR wallis[Text Word]) OR implant[Text Word]) OR ((microdiskectom*[Text Word] OR microdiscectom*[Text Word])))))))) NOT (cervical[Title] OR cervikal[Title])) Filters: Publication date from 2007/01/01 to 2020/12/31 395

Embase

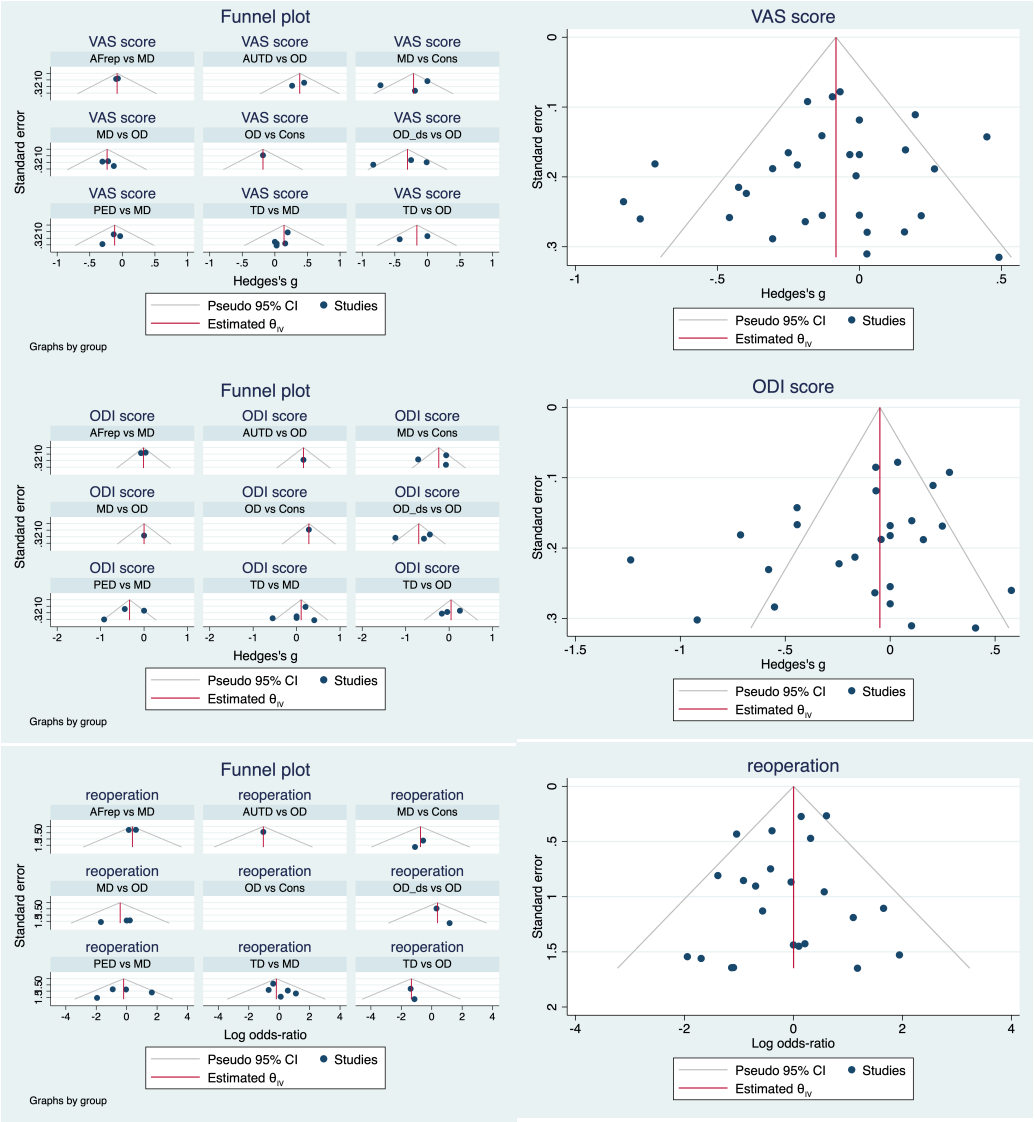
#21 #19 NOT #20 941
#20 cervical:ti OR cervikal:ti 132981
#19 #18 AND ('article'/it OR 'article in press'/it OR 'review'/it) 1116
#18 #11 AND #16 AND [2007-2020]/py 1337
#17 #11 AND #16 1806
#16 #12 OR #13 OR #14 OR #15 8027991
#15 (((single OR double OR triple) NEAR/2 (blind* OR mask*)):ti,ab,de) OR placebo:ti,ab,de 585632

#14	(((random* OR controlled* OR crossover OR 'cross over' OR blind* OR mask*) NEAR/3 (trial* OR study OR studies OR analy*)):ti,ab,de) OR rct:ti,ab,de	7875438
#13	'randomized controlled trial'/exp	596695
#12	'controlled clinical trial'/exp	767049
#11	#4 AND #10	6121
#10	#5 OR #6 OR #7 OR #8 OR #9	274829
#9	barricaid OR xclose OR dynesys OR wallis OR implant	262052
#8	(annulus OR annular) NEAR/2 (device* OR repair*)	384
#7	microdiscectom* OR microdiskectom* OR 'micro-discectom*' OR 'micro-diskectom*'	1376
#6	discectom* OR diskectom*	13199
#5	'discectomy'/exp	11298
#4	#1 OR #2 OR #3	30161
#3	(slipped OR displace* OR prolapse* OR hernia*) NEAR/2 (disc* OR disk*)	31352
#2	'lumbar disk hernia'/de	7068
#1	'intervertebral disk hernia'/de	18944

Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Intervertebral Disc Displacement] explode all trees	844
#2	((slipped OR displace* OR prolapse* OR hernia*) NEAR/2 (disc* OR disk*)):ti,ab,kw	2536
#3	#1 OR #2	2536
#4	MeSH descriptor: [Diskectomy] explode all trees	489
#5	(diskectom* OR discectom*):ti,ab,kw	1444
#6	(microdiskectom* OR microdiscectom* OR micro-diskectom* OR micro-discectom*):ti,ab,kw	246
#7	((annulus OR annular) NEAR/2 (device* OR repair*)):ti,ab,kw	31
#8	(barricaid OR xclose OR dynesys OR wallis OR implant):ti,ab,kw	13521
#9	(OR #4-#8)	14916
#10	#3 and #9 with Publication Year from 2007 to 2020, with Cochrane Library publication date Between Jan 2007 and Dec 2020, in Trials	521

Appendix B. Pairwise Meta-analysis



VAS score

Study	Treatment N	Treatment Mean	Treatment SD	Control N	Control Mean	Control SD	Hedges's g with 95% CI	Weight (%)
AFrep vs MD								
Bailey, 2013	478	1.5	2.79	249	1.7	3.22	-0.07 [-0.22, 0.09]	6.53
Thome, 2018	272	1.2	2.1	278	1.4	2.1	-0.10 [-0.26, 0.07]	6.38
Heterogeneity: τ^2 = 0.00, I^2 = 0.01%, H^2 = 1.00							-0.08 [-0.19, 0.03]	
Test of $\theta_i = \theta_j$: Q(1) = 0.06, p = 0.81								
AUTD vs OD								
Brouwer, 2015	55	1.81	2.3	57	1.26	1.81	0.26 [-0.11, 0.63]	4.05
Abrishamkar, 2015	100	3.04	2.57	100	2.14	1.17	0.45 [0.17, 0.73]	5.04
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							0.38 [0.16, 0.60]	
Test of $\theta_i = \theta_j$: Q(1) = 0.61, p = 0.44								
MD vs Cons								
Bailey, 2020	64	2.6	2.9	64	4.7	2.9	-0.72 [-1.08, -0.36]	4.20
Peul, 2007	141	1.1	2.25	142	1.1	2.26	0.00 [-0.23, 0.23]	5.61
Ostermann, 2006	28	.6	1.1	28	.9	1.9	-0.19 [-0.71, 0.33]	2.81
Heterogeneity: τ^2 = 0.12, I^2 = 79.15%, H^2 = 4.80							-0.30 [-0.75, 0.15]	
Test of $\theta_i = \theta_j$: Q(2) = 11.04, p = 0.00								
MD vs OD								
Tureyen, 2003	63	1.2	.75	51	1.4	.5	-0.31 [-0.67, 0.06]	4.06
Katayama, 2006	57	1.2	.4	62	1.3	.5	-0.22 [-0.58, 0.14]	4.17
Tullberg, 1993	30	2.1	1.51	30	2.3	1.51	-0.13 [-0.63, 0.37]	2.94
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							-0.23 [-0.46, -0.00]	
Test of $\theta_i = \theta_j$: Q(2) = 0.32, p = 0.85								
OD vs Cons								
Weinstein, 2006	232	2.13	2.73	240	2.63	2.74	-0.18 [-0.36, -0.00]	6.23
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2 = .							-0.18 [-0.36, -0.00]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
OD_ds vs OD								
Krappel, 2017	75	2.14	1.51	71	2.52	1.51	-0.25 [-0.57, 0.07]	4.53
Wu, 2017	50	2.05	1.68	50	2.07	1.71	-0.01 [-0.40, 0.38]	3.86
Gu, 2017	37	.94	.87	40	1.67	.87	-0.83 [-1.29, -0.37]	3.23
Heterogeneity: τ^2 = 0.12, I^2 = 75.37%, H^2 = 4.06							-0.35 [-0.80, 0.11]	
Test of $\theta_i = \theta_j$: Q(2) = 7.27, p = 0.03								
PED vs MD								
Gibson, 2017	70	2.6	3.1	70	2.7	2.8	-0.03 [-0.36, 0.30]	4.47
Meyer, 2020	23	2.1	1.9	24	3	3.6	-0.31 [-0.87, 0.26]	2.51
Ruetten, 2008	100	.9	1.51	100	1.1	1.51	-0.13 [-0.41, 0.14]	5.08
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							-0.12 [-0.32, 0.08]	
Test of $\theta_i = \theta_j$: Q(2) = 0.68, p = 0.71								
TD vs MD								
Righesso, 2007	21	1.17	.92	19	1.11	3.08	0.03 [-0.58, 0.63]	2.27
Franke (index), 2009	25	2.08	1.75	25	1.85	1	0.16 [-0.39, 0.71]	2.63
Arts, 2009	166	1.6	2.25	159	1.16	2.21	0.20 [-0.02, 0.41]	5.79
Ryang, 2008	30	2.1	2.4	30	2.1	2.4	0.00 [-0.50, 0.50]	2.94
Franke (transfer), 2009	27	1.6	2.34	23	1.54	1.92	0.03 [-0.52, 0.57]	2.62
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							0.14 [-0.03, 0.31]	
Test of $\theta_i = \theta_j$: Q(4) = 0.86, p = 0.93								
TD vs OD								
Teli, 2010	70	1	1	70	1	1	0.00 [-0.33, 0.33]	4.47
Yu, 2017	43	1.08	1.11	44	1.59	1.26	-0.43 [-0.85, -0.00]	3.57
Heterogeneity: τ^2 = 0.05, I^2 = 58.85%, H^2 = 2.43							-0.19 [-0.61, 0.22]	
Test of $\theta_i = \theta_j$: Q(1) = 2.43, p = 0.12								
Overall							-0.10 [-0.21, 0.01]	
Heterogeneity: τ^2 = 0.04, I^2 = 63.99%, H^2 = 2.78								
Test of $\theta_i = \theta_j$: Q(23) = 55.79, p = 0.00								
Test of group differences: $Q_b(8)$ = 27.76, p = 0.00								

-2 -1 0 1

Random-effects REML model

ODI score

Study	Treatment N	Treatment Mean	Treatment SD	Control N	Control Mean	Control SD	Hedges's g with 95% CI	Weight (%)
AFrep vs MD								
Bailey, 2013	478	20.9	26.2	249	20	23.3	0.04 [-0.12, 0.19]	5.70
Thome, 2018	272	13	14	278	14	15	-0.07 [-0.24, 0.10]	5.65
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00							-0.01 [-0.12, 0.10]	
Test of $\theta_i = \theta_j$: Q(1) = 0.82, p = 0.37								
AUTD vs OD								
Brouwer, 2015	55	5.4	7.3	57	4.4	5.1	0.16 [-0.21, 0.53]	4.61
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2 = .							0.16 [-0.21, 0.53]	
Test of $\theta_i = \theta_j$: Q(0) = -0.00, p = .								
MD vs Cons								
Bailey, 2020	64	22.9	16.4	64	34.7	16.5	-0.71 [-1.07, -0.36]	4.68
Peul, 2007	141	3.3	5.9	142	3.7	5.9	-0.07 [-0.30, 0.16]	5.35
Ostermann, 2006	28	10	13	28	11	14	-0.07 [-0.59, 0.44]	3.76
Heterogeneity: τ^2 = 0.11, I^2 = 77.21%, H^2 = 4.39							-0.29 [-0.72, 0.14]	
Test of $\theta_i = \theta_j$: Q(2) = 9.32, p = 0.01								
MD vs OD								
Katayama, 2006	57	27	1	62	27	2	0.00 [-0.36, 0.36]	4.67
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2 = .							0.00 [-0.36, 0.36]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
OD vs Cons								
Weinstein, 2006	232	20.6	18.8	240	15	20.7	0.28 [0.10, 0.46]	5.59
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2 = .							0.28 [0.10, 0.46]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .								
OD_ds vs OD								
Krappel, 2017	75	15.63	8.98	71	19.63	8.98	-0.44 [-0.77, -0.12]	4.85
Wu, 2017	50	5.61	3.15	50	11.38	5.74	-1.24 [-1.66, -0.81]	4.28
Gu, 2017	37	12.18	12.4	40	19.44	12.41	-0.58 [-1.03, -0.13]	4.12
Heterogeneity: τ^2 = 0.14, I^2 = 77.04%, H^2 = 4.35							-0.74 [-1.22, -0.26]	
Test of $\theta_i = \theta_j$: Q(2) = 8.77, p = 0.01								
PED vs MD								
Gibson, 2017	70	22	20	70	22	19	0.00 [-0.33, 0.33]	4.83
Meyer, 2020	23	20.7	8.98	24	29.1	8.98	-0.92 [-1.51, -0.33]	3.37
Ruetten, 2008	100	19	8.98	100	23	8.98	-0.44 [-0.72, -0.16]	5.11
Heterogeneity: τ^2 = 0.14, I^2 = 79.52%, H^2 = 4.88							-0.41 [-0.89, 0.07]	
Test of $\theta_i = \theta_j$: Q(2) = 8.30, p = 0.02								
TD vs MD								
Righesso, 2007	21	12.94	10.46	19	9.33	6.17	0.41 [-0.21, 1.02]	3.26
Franke (index), 2009	25	8.8	9.5	25	15.5	14	-0.55 [-1.11, 0.01]	3.55
Arts, 2009	166	4.7	6.4	159	3.4	6.3	0.20 [-0.01, 0.42]	5.43
Ryang, 2008	30	12	14	30	12	18.8	0.00 [-0.50, 0.50]	3.86
Franke (transfer), 2009	27	12.17	14.8	23	12.17	13.7	0.00 [-0.55, 0.55]	3.60
Heterogeneity: τ^2 = 0.04, I^2 = 44.62%, H^2 = 1.81							0.04 [-0.23, 0.32]	
Test of $\theta_i = \theta_j$: Q(4) = 7.38, p = 0.12								
TD vs OD								
Teli, 2010	70	14	4	70	13	4	0.25 [-0.08, 0.58]	4.82
Yu, 2017	43	13.1	7.17	44	14.41	8.24	-0.17 [-0.59, 0.25]	4.32
Garg, 2011	55	1.75	8.98	57	2.14	8.98	-0.04 [-0.41, 0.32]	4.61
Heterogeneity: τ^2 = 0.01, I^2 = 27.15%, H^2 = 1.37							0.04 [-0.21, 0.29]	
Test of $\theta_i = \theta_j$: Q(2) = 2.68, p = 0.26								
Overall							-0.16 [-0.33, 0.00]	
Heterogeneity: τ^2 = 0.12, I^2 = 83.34%, H^2 = 6.00								
Test of $\theta_i = \theta_j$: Q(21) = 99.53, p = 0.00								
Test of group differences: $Q_b(8)$ = 23.68, p = 0.00								

-2 -1 0 1

Random-effects REML model

reoperation

Study	Treatment Yes	Treatment No	Control Yes	Control No	Log Odds-Ratio with 95% CI	Weight (%)
AFrep vs MD						
Bailey, 2013	401	39	214	24	0.14 [-0.39, 0.68]	14.54
Thome, 2018	272	24	278	45	0.61 [0.08, 1.13]	14.73
Heterogeneity: τ^2 = 0.03, I^2 = 32.45%, H^2 = 1.48					0.38 [-0.08, 0.83]	
Test of $\theta_i = \theta_j$: Q(1) = 1.48, p = 0.22						
AUTD vs OD						
Brouwer, 2015	54	26	53	9	-1.04 [-1.89, -0.19]	10.23
Heterogeneity: τ^2 = 0.00, I^2 = .%, H^2 = .					-1.04 [-1.89, -0.19]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .						
MD vs Cons						
Bailey, 2020	64	1	64	0	-1.10 [-4.32, 2.12]	1.34
Peul, 2007	125	4	55	1	-0.57 [-2.78, 1.65]	2.64
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					-0.74 [-2.56, 1.09]	
Test of $\theta_i = \theta_j$: Q(1) = 0.07, p = 0.79						
MD vs OD						
Tureyen, 2003	63	1	51	1	0.21 [-2.58, 3.01]	1.74
Katayama, 2006	57	2	62	0	-1.69 [-4.75, 1.36]	1.48
Tullberg, 1993	30	1	30	1	0.00 [-2.82, 2.82]	1.72
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					-0.43 [-2.09, 1.24]	
Test of $\theta_i = \theta_j$: Q(2) = 0.95, p = 0.62						
OD_ds vs OD						
Krappel, 2017	73	9	71	12	0.32 [-0.61, 1.24]	9.36
Gu, 2017	40	0	37	1	1.18 [-2.06, 4.41]	1.33
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					0.38 [-0.51, 1.27]	
Test of $\theta_i = \theta_j$: Q(1) = 0.25, p = 0.62						
PED vs MD						
Mayer, 1993	20	3	20	0	-1.95 [-4.97, 1.08]	1.51
Gibson, 2017	70	5	70	2	-0.92 [-2.59, 0.76]	4.21
Meyer, 2020	23	3	24	3	-0.04 [-1.74, 1.66]	4.11
Ruetten, 2008	91	1	87	5	1.65 [-0.51, 3.82]	2.74
Heterogeneity: τ^2 = 0.54, I^2 = 33.34%, H^2 = 1.50					-0.20 [-1.44, 1.05]	
Test of $\theta_i = \theta_j$: Q(3) = 4.83, p = 0.18						
TD vs MD						
Righesso, 2007	21	1	19	1	0.10 [-2.74, 2.94]	1.69
Franke (index), 2009	25	1	25	3	1.10 [-1.23, 3.43]	2.42
Arts, 2009	166	17	159	11	-0.39 [-1.18, 0.40]	10.95
Ryang, 2008	30	4	30	2	-0.69 [-2.46, 1.08]	3.84
Franke (transfer), 2009	27	2	23	3	0.57 [-1.31, 2.44]	3.51
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					-0.19 [-0.82, 0.44]	
Test of $\theta_i = \theta_j$: Q(4) = 2.40, p = 0.66						
TD vs OD						
Teli, 2010	70	8	70	2	-1.39 [-2.97, 0.20]	4.58
Garg, 2011	55	1	57	0	-1.13 [-4.36, 2.09]	1.34
Heterogeneity: τ^2 = 0.00, I^2 = 0.00%, H^2 = 1.00					-1.34 [-2.76, 0.08]	
Test of $\theta_i = \theta_j$: Q(1) = 0.02, p = 0.89						
Overall					-0.13 [-0.51, 0.26]	
Heterogeneity: τ^2 = 0.19, I^2 = 31.20%, H^2 = 1.45						
Test of $\theta_i = \theta_j$: Q(20) = 25.26, p = 0.19						
Test of group differences: $Q_b(7)$ = 13.69, p = 0.06						

-5 0 5

Random-effects REML model

Appendix C. Adverse Events

Serious Adverse Events

There were 4 serious adverse events. The number of participants affected was 4 of 20 or 20%:

Event	Body System	Intensity	Start Date	Stop Date	Action Taken	Outcome	Causality wrt to	Patient No
Cholelithiasis	Hepatobiliary disorder	Moderate	15/10/2013	10/06/2013	Drug Treatment	Recovered	Not Related	10
Ileus	Gastrointestinal disorder	Moderate	12/06/2014	14/06/2014	Drug Treatment	Recovered	Not Related	13
Intervertebral disc protrusion	Intervertebral disc protrusion	Moderate	11/06/2013	11/06/2013	Reoperation	Recovered with sequelae	Not Related	07
Hyperglycemia	Metabolism and nutrition disorders	Mild	12/12/2012	15/12/2012	Drug Treatment	Recovered	Not Related	03

Significant Adverse Events

There were 3 significant adverse events; the number of participants affected was 3 of 20 or 15%:

Event	Body System	Intensity	Start Date	Stop Date	Action Taken	Outcome	Causality wrt to	Patient No
Back Pain	Musculoskeletal and connective tissue disorder	Moderate	01/10/2013	22/10/2014	Drug Treatment	Recovered	Not Related	02
Dysaesthesia	Nervous system disorder	Moderate	07/03/2014	NA	None	Not recovered	Not Related	18
Extremity Pain	Musculoskeletal and connective tissue disorders	Moderate	Unk/01/2014	NA	Drug Treatment	Not recovered	Not Related	10

Other Significant Adverse Events

There were 10 other significant adverse events; 10 of 20 (50%) of participants were affected:

Event	Body System	Intensity	Start Date	Stop Date	Action Taken	Outcome	Causality wrt to	Patient No
Arthralgia	General disorders& administration site condition	Mild	10/09/2013	NA	None	Not Recovered	Not Related	03
Cystitis	Infection/ Infestation	Mild	12/06/2014	14/06/2014	Drug Treatment	Recovered	Not Related	07
Back Pain	Musculoskeletal and connective tissue disorders	Mild	05/11/2013	23/09/2014	Drug Treatment	Recovered	Not Related	13
Back Pain	Musculoskeletal and connective tissue disorders	Mild	28/11/2013	24/12/2013	Drug Treatment	Recovered	Not Related	14
Back Pain	Musculoskeletal and connective tissue disorders	Mild	12/20/2014	NA	Drug Treatment	Not Recovered	Not Related	16
Extremity Pain	Musculoskeletal and connective tissue disorders	Mild	15/04/2014	23/09/2014	Drug Treatment	Recovered	Not Related	13
Gastrointestinal Pain	Gastrointestinal disorder	Mild	Unk/04/2014	Unk/05/2014	Drug Treatment	Recovered	Not Related	20
Pneumonia	Infection/ Infestation	Mild	Unk/02/2015	Unk/03/2015	Drug Treatment	Recovered	Not Related	17

Surgical Site Infection	Infection/ Infestation	Mild	30/01/2014	08/02/2014	Drug Treatment	Recovered	Not Related	15
Surgical Site Infection	Infection/ Infestation	Mild	Unk/04/2014	Unk/04/2014	Drug Treatment	Recovered	Not Related	19

ISSN (online): 2246-1302
ISBN (online): 978-87-7210-938-1

AALBORG UNIVERSITY PRESS