Concept models of new fixation and stabilization methods for osteoporotic vertebrae

What are new methods for stabilizing osteoporotic vertebral compression fractures and fixating the vertebrae, what do concept models of the best new methods look like and how do they compare to current methods and methods being developed?

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Preface

This thesis is written as a final assignment for the Bachelor's degree of Technical Medicine. We would like to thank our supervisors, prof.dr.ir. G.J. Verkerke, dr. M.C. Kruyt and ir. E.E.G. Hekman, for their guidance in this study and their help when it comes to content related problems. Furthermore, we would like to thank our tutor, M.D. Van der Stoel, for helping us bring this project successfully to an end when it comes to process related matters. We want to give special thanks to prof.dr.ir. G.J. Verkerke for submitting this assignment, which allowed us to develop ourselves in the field of managing osteoporotic vertebral fractures. Please enjoy reading our thesis!

Abstract

***Introduction**:* As the population ages, osteoporosis becomes a more and more common geriatric disease. The balance of the bone-remodeling cycle is disturbed, which causes it to become brittle and eventually break. This research focuses on osteoporotic vertebral compression fractures (OVCF). Commonly used methods are a pedicle screw (PS) system, vertebro- and kyphoplasty (VP and BKP), and vertebral body stenting (VBS).

Problem: PS systems present themselves with pull-out problems, leakage of poly(methyl methacrylate) (PMMA) into the spinal canal and adjacent level vertebral fractures (ALVFs). Leakage of PMMA into the spinal canal and ALVFs are also present in VP, BKP and VBS. Besides, VP and BKP have not been proven to be more effective than placebos. The removal of PMMA out of the vertebra when infected is also very difficult.

***Method**:* First, requirements were drawn up by brainstorming and an interview with a medic, thereafter, extensive literature review was done to assess current methods and and subsequently, several ideas were drawn up by brainstorming, of which the best were finally worked out into a concept model.

***Results**:* The set requirements needed for a new method were determined to be safe, effective, non-invasive, durable, user-friendly, affordable and universal. Several methods have been found in literature, the best seeming to be stem cells. Also, several methods have been drawn up by brainstorming, varying from magnets to 3D printed molds. The most promising methods, being crisscross fixation in combination with spinal loop rectangle (CC-SLR), with and without PSs and an inflatable ball filled with fluid or little cement balls in the vertebral body, are being assessed on the basis of the requirements.

***Discussion**:* Since some components are established by means of brainstorming, these are not complete and can be complemented. The literature review was extensive, but could always be done more extensively. Only methods for fixating or stabilizing ordinary OVCFs have been thought of, while often more complications are present in case of the need of fixation. Also, this research focuses on elderly, while there are some children with this disease, who need better integration of the material with the surrounding tissue. A lot of research still has to be done before one of these methods could be implemented, mostly on finding a fitting material, and thereafter assessing the effectivity of the method in a model.

***Conclusion**:* Of the new methods that were suggested in this study, CC-SLR, CC-SLR in combination with PSs, an inflatable ball filled with fluid or little cement balls in the vertebral body are the best. These methods should be researched further before they could become applicable.

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1 Introduction

As the population ages, geriatric diseases, among which osteoporosis, become more and more common. [1] Osteoporosis is a decrease in bone mass and disruption of bone architecture, caused by a disturbed balance of the remodeling cycle. [2] Osteoporosis will occur to a greater or lesser extent as the age progresses. From the age of 40, bone mass decreases 0.3-0.5% every year. In postmenopausal women, this can mount up to 2-3% per year. [3] This results in a decrease of bone strength, causing an increased incidence of bone fractures. [4]

Two types of osteoporosis exist, namely primary and secondary osteoporosis. Primary osteoporosis can be divided into two types. Type 1 primary osteoporosis is caused by an increase of osteoclast activity induced by a consistent decrease of estrogen, which starts in menopause. This decrease leads to secretion of cytokines, including IL-1, IL-6 and TNF, that attract and activate osteoclasts. Type 2 primary osteoporosis is caused by aging induced by a decreased osteoblast function and to a lesser extent an increased osteoclast activity. Type 1 and type 2 primary osteoporosis histologically show respectively disturbed connections between trabeculae and thinned trabeculae. Secondary osteoporosis is connected to a specific cause, such as endocrine or genetic diseases. Secondary osteoporosis histologically shows disturbed connections between trabeculae and a decreased amount of trabeculae, which are also thinned. [2]

Osteoporosis is diagnosed by measuring the bone mineral density (BMD) in mg/cm^3, and converting this to a T-score. This T-score can be calculated by subtracting the average BMD-value of a young, normal reference population from the patient's BMD-value. This has to be divided by the standard deviation of the reference population. In formula, this is: T-score = (BMD - BMDref)/SDref. The World Health Organization categorizes a T-score above -1.0 as normal, between -1.0 and -2.5 as osteopenia, the progenitor of osteoporosis, and below -2.5 as osteoporosis. If a patient is older than 60 and has a T-score below -2.5, a vertebral fracture assessment should be done. Formerly, the Z-score was used to diagnose osteoporosis, were the reference population consists of people of the same age and sex. Currently, this is no longer used, since the risk of fractures is more important than the deviation relative to peers. [5]

The prevalence of osteoporosis found in the Netherlands is 7.5 per 1,000 men and 43.1 per 1,000 women and increases greatly with age. At the age of 70 for instance, the prevalence found is 25.7 per 1,000 men and 153.0 per 1,000 women. This is probably an underestimation of the true prevalence though, as many people do not experience symptoms of osteoporosis. [6] One of these symptoms is pain following a vertebral fracture. 6,744 vertebral fractures occurred in the Netherlands in 2010, of which 46% (3,115 fractures) was caused by osteoporosis. When considering the aging of the population, the number of fractures caused by osteoporosis is estimated to increase by 40% in the time period 2010 to 2030 in the Netherlands. [1]

This study will focus on the treatment of thoracolumbar osteoporotic vertebral compression fractures (OVCFs) in elderly. This point of focus is chosen because of the patients with osteoporosis, elderly are the most common. Also, there are several challenges when it comes to treating OVCFs and most fractures due to osteoporosis are thoracolumbar. [7] When an OVCF causes extreme pain and the patient does not respond to conservative treatment, fixation of this vertebra should be considered. [8] The vertebra is currently fixated with either vertebroplasty (VP) or balloon kyphoplasty (BKP), both using poly(methyl methacrylate) (PMMA), or a pedicle screw (PS) system, possibly in combination with PMMA or vertebral body stenting (VBS). [Dr. M.C. Kruyt, personal communication, 06/01/2018] [8][9][10] The insertion of PMMA in the vertebral body is not preferred because of the multiple disadvantages the material can present, [11][12] among which leakage of

PMMA in the spinal canal and difficulty with removing PMMA when infected. [Dr. M.C. Kruyt, personal communication, 06/01/2018] However, the use of solely a PS system is neither sufficient, because the osteoporotic bone is no longer strong enough to hold the screws [13] and thus the system pulls out. This often causes adjacent level vertebral fractures (ALVFs) which leads to progressive kyphosis. [14] The goal of this research is therefore designing a new method for stabilizing OVCFs and fixating the vertebrae.

2 Current methods
Most of the time, conservative treatment, consisting of medication, is sufficient in case of an OVCF. However, when there is a kyphosis of more than 20^{o}, or extreme pain, a non-medicational method may be used. [9] In this paragraph an overview of the current non-medicational methods, VP, BKP, PS and VBS systems, is given.

2.1 Vertebroplasty and balloon kyphoplasty
To stabilize an OVCF, VP or BKP can be used. VP is the CT fluoroscopy-guided insertion of PMMA into the porous bone. [15] In contrast to VP, in BKP a balloon is inflated in the porous bone to restore height, before inserting PMMA. [16] These methods are very similar, in both a relief of pain occurs and both are relatively safe. However, there are small differences. BKP provides, as said, a restorage of height. It is still unclear whether this has any clinical advantages. BKP also has an increased operation time, due to inflation of the balloon, slightly longer fracture free survival, slightly less PMMA migration [17] and much higher material costs compared to VP. [18]

PMMA is made of two components, a PMMA powder and a liquid methyl methacrylate (MMA) solution. When these are mixed, the monomers will polymerise, and subsequently, PMMA hardens. [19] MMA is cytotoxic and can cause cardiovascular problems as well as hypoxia. It can also dissolve fat from cell membranes and therefore cause an embolism. [12][20] The polymerization of MMA releases heat (70-79^{o}C), which causes necrosis in the surrounding tissue. [21] Next, a phase of cicatrisation is followed by tissue granulation. This tissue granulation is a characteristic of chronic inflammation. [22] PMMA does not integrate well with surrounding tissue because of a lack of bioactivity, high elastic modulus relative to that of the contiguous bone and a shrinkage of PMMA after polymerization, of up to 7.3%. [12][21] In the course of time fatigue of the material can occur, which could lead to new fractures. [12]

It is not clear whether VP is more effective than a placebo procedure. Several studies found no demonstrable clinically important benefits of VP in comparison to a placebo procedure, [23][24][25] while other studies found VP to be superior to a placebo procedure. [26][27] Since VP and BKP are similar when it comes to terms of function restoration and pain relief [24][25][28] it is as well questionable whether BKP is effective.

VP and BKP are relatively easy and minimally invasive methods, [27][28] both causing a bone-PMMA interface, which can lead to ALVFs. [Dr. M.C, Kruyt, personal communication, 06/01/2018] The methods have a blood loss of respectively 215 +/- 85 mL and 265 +/- 25 mL, [30] and are universally applicable, except for the contraindications of active infection, cement allergy and coagulation disorders [31] and have a lifespan of at least 30 years. [32]

According to many studies, VP is as safe as conservative treatment since no significant increase in adverse events has been found. [23][24][26] The main complications associated with VP are PMMA leakage, pulmonary cement embolisms and ALVFs. [24][25] PMMA leakage occurs in 1% to 48% of all cases, pulmonary cement embolisms in 0.6% to 4.6% [28][33] and ALVFs in 8% to 52%. [28]

One big advantage of BKP compared to VP is the use of high viscosity PMMA under low pressure instead of low viscosity PMMA under high pressure. This reduces the rate of inadvertent placement of PMMA. [25] In BKP, the rates of PMMA leakage range from 2% to 24%, [33][34][35] of pulmonary cement embolisms from 0.01% to 1.7% [19] and of ALVFs from 3% to 29%. [28] Furthermore, BKP requires general anesthesia whereas VP only requires local anesthesia. [25] Even though BKP has lower complication rates, Doidge et al. found no significant differences between the safety of VP and BKP. [24]

According to Mehio et al., mean inpatient and outpatient costs are respectively $11,386 and $2,997 for VP, with a mean operation cost of $1,175.78, while mean inpatient and outpatient costs are respectively $16,182 and $7,010 for BKP, with a mean operation cost of $1,901.12. [36]

2.2 Pedicle screw system

A PS system is currently the main treatment for specific, high grade OVCFs in UMC Utrecht. [Dr. M.C. Kruyt, personal communication, 06/01/2018] The goal of a PS system is spinal fusion and thereby stabilization. [37] Bone grafts causing ossification are not applied in UMC Utrecht, but are used in other practices, the process will therefore be described below. Hereafter, it is described how this will be reached. Subsequently, the recent developments will be mentioned and finally, advantages and disadvantages will be given.

2.2.1 Ossification

The ossification of the intervertebral disc could help accommodate stabilization. Ossification occurs when a bone graft is implanted. During ossification, two processes take place: intramembranous ossification and endochondral ossification. The first uses surrounding tissue and differentiation of mesenchymal cells into osteoblasts to form bone tissue. The second uses cartilage as a mean to grow bone tissue. After implantation of the bone graft intramembranous ossification will occur close to the original bone and endochondral ossification in the middle of the graft. The intramembranous ossification will eventually spread over the whole graft. [38][39] In the case of osteoporosis spinal fusion often fails, because the bone's growth capacity is not enough. [38][40]

2.2.2 Systems

The goal of spinal fusion is fixation and the absence of pain. [37] This is realized by a bilateral PS system. [13][41]

With this intervention the vertebrae that need to fuse will first be decorticated, which is the removal of cortical bone. [38][42] Subsequently, screws are bilaterally placed into the pedicles, after which bilateral rods, aligned along the vertebrae, are attached to the screws, as seen in figure 1. [13] Next, a bone graft could be placed in one of two possible locations. The graft can be placed between the vertebral bodies, in an interbody fusion cage, which will fuse the vertebrae by ossificating the intervertebral disc, [43] or posterior of the vertebrae, causing the transverse processes to unify. Depending on the location of the graft, the tissue will be obtained from either the facet joint or the pelvis. [38][42] A combination of both locations is also possible. However, there are no proven advantages of using a combination instead of one of both locations. [44]

Figure 1: Pedicle screw system with bone graft in interbody cage [105]

PMMA can be used to enhance the PS connection. This is realized by pouring the PMMA through holes in the screw, [11] which improves the biomechanical stability and pull-out strength. [20] Use of PMMA augmentation in PS fixation is advised when the BMD is lower than 80 mg/cm^3, which is the threshold for osteoporosis according to Weiser et al. [45] To improve the pull-out strength even more, a combination of PMMA with an expandable screw can be used. This screw has a cannulated center, in which an expansion pin is placed which causes the bottom of the screw to expand. [46]

2.2.3 Advantages and disadvantages of pedicle screw systems

The symptomatic complication rate for PS systems is 54% for open back surgery [47] and 18% for a percutaneous procedure. [48] The main complications associated with a PS system without PMMA include screw pull-out (62.8%), [49] caused by low bone quality, and non-union (5-35%), caused by reduced osteoblast ability, poor vascularity and lower bone marrow quality in the host bed. [13][38] Other, less common complications include deep wound infection (1.5-4.7%), [47] deep vein thrombosis (1.6%), [41] and intraoperative pedicle fracture (1.1-13%). [41][50] In a system using PMMA, the screw pull-out is 4.3% [49] and PMMA leakage is 72.2%, of which 5.5% symptomatic. [11] The incidence of non-union lays within the same range as without PMMA, [51] considering it does not depend on the use of PMMA. Other complications are intraoperative blockade of the screw locking mechanism (9.2%) [52] and postoperative atelectasis (11.2%). [53] Complications that occur in both with and without PMMA include screw fracture (respectively 3-5.7% and 5.6%), [47][50][53] nerve injury (respectively 0.04-3.24% and 0.5-3.7%) [41][50][54] and pulmonary embolism (respectively 2.2% and 4.1%) [41][52] PS fixation increases the risk of ALVFs, [55] but it is unclear whether a fracture is a consequence of the method, since vertebral fractures occur regularly with osteoporosis. [56] Therefore the risk due to the method is not known. Even though many complications can occur, PS fixation is still considered a safe technique to achieve a stable situation after an OVCF. [49] It is, however, an invasive technique in comparison with VP and BKP, with a blood loss of 824 +/- 440 mL. [57]

Screw pull-out or non-union often lead to unsatisfactory clinical outcomes. The use of PS fixation in OVCFs is therefore not as effective as wished. [13][38] In a study of Janssen et al. a 30-day mortality rate of 1.8% is found. [11]

A PS system is universally applicable, except for comorbidities such as cardiopulmonary disease, renal disease, diabetes mellitus and nutritional disorders, which can negatively affect the surgical outcome. [38] Nowadays, PS fixation is frequently used, so surgeons know how to perform this. A poor screw placement appeared in only 1.6% of all cases, so overall it is a user-friendly method. [58] The costs of PS fixation are $6,109 for an average of 2.6 vertebrae. [59] PS systems have been applied in many patients, some as young as 2 years. Systems will only be removed when they cause complications. [Dr. M.C. Kruyt, personal communication, 06/01/2018] This suggests the result of PS fixation has a long lifespan when no complications occur.

2.3 Vertebral body stenting

In UMC Utrecht, a PS system is combined with the use of VBS in a fractured vertebra, where two stents are inserted through working sleeves to create a pre-cavity. Thereafter, PMMA is injected through the working sleeves into the stents and enhances the strength of the vertebral body. [60] VBS is similar to BKP and thus has the same invasiveness and safety. [61] Also, the risk of ALVFs is similar to BKP. [62] The only difference in effectiveness is the height loss after deflation. When using BKP, a height loss of 2.2 +/- 1.1 mm is seen while VBS shows a height loss of 0.7 +/- 0.7 mm. [61] The clinical importance of this difference in height loss needs more research, since data from Rohlmann et al. suggests that this difference can be clinically relevant, [63] while Baheti et al. described controversy on the clinical relevance of height restoration. [17] The material costs for one vertebra are $3,750 and for two or three vertebrae, these costs are respectively $6,950 and $10,400. VBS was associated with significantly higher pressures during balloon inflation and remarkably more material-related complications like incomplete or no opening of the stent and balloon rupture than BKP. [64] VBS is a user-friendly and universal method because it is similar to BKP. Nothing can be said about the durability yet.

3 Problem statement

PS systems come with pull-out problems and leakage of PMMA into the spinal canal. Additionally, even though VBS does stabilize the OVCF, leakage of PMMA into the spinal canal is present and the bone-PMMA interface causes ALVFs. Furthermore, in VP and BKP this leakage and interface are also present and they have not been proven to be more effective than conservative treatment. The removal of PMMA when infected is also very difficult.

The goal of this research is therefore to design a new method for stabilizing the OVCF and fixating the vertebrae. The main question raised is: What are new methods for stabilizing osteoporotic vertebral compression fractures and fixating the vertebrae, what do concept models of the best new methods look like and how do they compare to current methods and methods being developed?

Subquestions are:

1. What requirements does a new method have to meet based on brainstorm-sessions and interviews with medics?
2. What methods being developed could offer an improvement compared to the current method for stabilizing OVCFs and fixating the vertebrae and to what extent do they meet the requirements?
3. What could new ideas, including improvements of the methods found in subquestion 2, retrieved from brainstorm-sessions, look like and which of these is or are best?
4. What do concept models of the best fixation methods of subquestion 3 look like and to what extent do they meet the requirements?

4 Methods

Since many abbreviations are used in this study, a list of those abbreviations has been made. This can be found in appendix A.

Requirements to fixate OVCFs have been drawn up with the help of literature study, an interview and brainstorming sessions. The interview questions can be found in appendix B, written down in Dutch. Hereafter a weight has been given to each requirement so that more important requirements are weighed more heavily than less important requirements. To achieve this, each member of the research group gave the requirements a weight of 1 to 4, where 4 is the highest weight. Afterwards, this has been discussed and an agreement has been reached about what the weight of each requirement should be.

Research has extensively been conducted in literature on what methods were already in development. Several methods have been found and these were assessed on the extent to which they meet the earlier drawn up requirements. A table with grades for each requirement per method has been made, based on the known facts in literature. The grades differ from 1 to 10, where 1 means it is not meeting the requirement and 10 means the requirement is completely met. Current methods are also included in this table, to be able to compare them. To get to the grades, each member of the research group gave the methods a grade for each requirement. The averages of these grades were calculated and rounded to one decimal. When facts were missing, each member made an estimation of the correct grade.

By means of brainstorming sessions, it has been attempted to find new methods with as much advantages and as few disadvantages as possible by bringing up new ideas or improving or combining methods described in subquestion 2. The new ideas have been assessed with respect to each other on the basis of the requirements. Some ideas have been worked out with the use of SketchBook (Autodesk, Boston) [65] all in the same image, which is shown in figure 2. One idea has been worked out with the use of SolidWorks (Dassault Systèmes, Waltham) [66] Based on the requirements, several ideas could be discarded and three methods were left.

These three methods have each been elaborated into a concept model with a more extensive description and sketch of the methods. Among others, materials, insertion manner, operation procedure and expected complications have been researched and are described. A table with grades for each requirement per method has been made in the same manner as the table for methods in development. Finally, these grades were compared to the grades of the current methods and the methods in development.

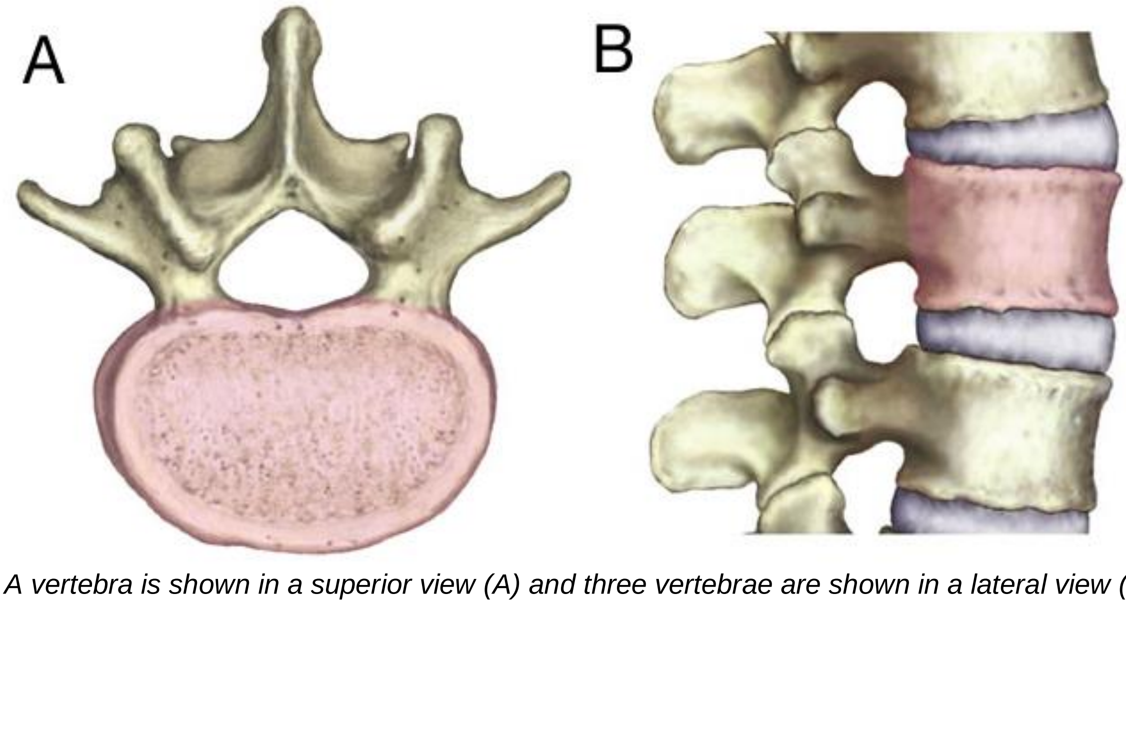

Figure 2: A vertebra is shown in a superior view (A) and three vertebrae are shown in a lateral view (B). [106]

5 Requirements

What requirements does a new method have to meet based on brainstorm-sessions and interviews with medics?

To determine what method is the best option to treat an OVCF, new methods should be assessed on the basis of a list of requirements. Some requirements are more important than others, so the weight of importance is also determined. The following requirements were obtained.

5.1 Safety
First and foremost, a method should be safe, [67] meaning it has to have a low complication and mortality rate. Furthermore, the consequences of complications should be taken into account. A new method should be safer or as safe as the current method to be considered in medical practice. This means a new method should have a mortality and complication rate lower than or similar to the current method.

5.2 Effectiveness
A new method should of course be as effective as or more effective than the current method. [67] The goal of a method is relief of pain, but also stabilization of the vertebrae, and thus improved balance. The method does not have to prevent fractures, but more importantly, it should not promote ALVFs more than the current method.

5.3 Invasiveness
Most patients undergoing a treatment for OVCF are elderly. A new method should therefore be as minimally invasive as possible, thus gaining a short recovery time. Due to this shorter recovery time, the impact on patients will be smaller. A minimally invasive method includes small wounds and little blood loss. The method should also not need intensive maintenance or many revisits, to reduce the impact on the patients.

5.4 Durability
Since this research focuses on elderly, the method does not have to last a lifetime. However, it should last for the rest of their lives, so a durability of 30 years would be enough. When it comes to degradable materials, a new method should last until the fracture has healed, which is 1 year on average. [Dr. M.C. Kruyt, personal communication, 06/01/2018]

5.5 User-friendliness
It should be possible to learn implementing this new method without much effort. Only if the method leads to a big improvement, effort could be made. If the method leads to only a small improvement, though, it should not cost much effort to learn. User-friendliness is difficult to measure, but the time to learn the procedure of different methods could be compared to each other.

5.6 Affordability
The new method should not be much more expensive than the current method. To keep a new method affordable, the operation time and material costs should be comparable with or less than the current method.

5.7 Universality
A new method should be universal, meaning it can be applied to all or most patients, to help as many patients as possible. It will also be more cost-efficient when many patients can be treated with the same surgery, because the knowledge and material will be present.

5.8 Weight

To assess the importance of the different requirements, a weight is given to each requirement. In table 1, these given weights are shown.

Table 1: Requirements with given weights

Requirement	**Weight**
Safety	4x
Effectiveness	4x
Invasiveness	3x
Durability	2x
User-friendliness	2x
Affordability	2x
Universality	1x

6 Stabilization and fixation methods in development

What methods being developed could offer an improvement compared to the current method for stabilizing OVCFs and fixating the vertebrae and to what extent do they meet the requirements?

Different experimental methods for stabilization of OVCFs and fixation of the vertebrae described in literature are summed up and explained below. To see which method would be best, they are assessed on the basis of the requirements drawn up before, and have been given grades according to the extent to which they meet the requirements. An overview of these grades is given in table 2.

6.1 Wiring

Posterior fixation using wires has already been used in treatments, for instance of cervical spine trauma. Wiring fixates flexion of the spine and can only be used if the lamina, facet joints or spinous processes are preserved. [68]

6.1.1 Crisscross fixation

A fixation technique that includes wiring is Cahill's fixation in which the spinous processes and facets are wired together. A hole is drilled in the superior articular facet and a wire is passed through. The wire is then looped around the spinous process of the vertebra underneath. To achieve full fixation, this is repeated on the contralateral side. [69]

Very similar to Cahill's fixation is crisscross (CC) fixation. Currently, the use of CC fixation has only been researched for resolving biomechanical effects caused by multilevel cervical laminectomy. When administering CC fixation, wires are passed through drilled holes in the superior articular facet and are secured in a cinch and crimp technique. Labelling of the wires is done in a sequential cranial-caudal pattern. In figure 3, the wires are shown with their corresponding numbers. Wires 1 and 3 are connected, as well as wires 2 and 5 and wires 4 and 6. Wire 6 is passed around the spinous process below the vertebrae that need fixation before being connected to wire 4. Tightening of the connection between wires 4 and 6 secures connections across all the facet joints. Stress points in this system are the cranial and caudal connections. These stress points are mitigated by inclusion of a small button cranially and double crimps caudally. Even though figure 3 only shows wires on one side, the method is performed bilaterally. [70]

Cusick et al. found a strength of CC fixation comparable to bilateral PS systems in this application. Furthermore, CC fixation shows a more consistent stiffness than PS fixation. PS fixation might therefore lead to greater stresses on adjacent vertebrae than CC fixation. [70] This means CC fixation in normal bone is at least as effective as PS fixation, if not more. However, even though the facet joints and spinous processes are usually preserved in osteoporosis, which is needed for CC fixation, the disease is a contraindication for posterior fixation using wiring in general as the procedure is at risk for failing in osteoporotic bone. [68] Given this, the effectiveness of CC fixation in osteoporotic bone can be questioned. Nevertheless, CC fixation reaches constant bicortical fixation with minimal involvement of cancellous bone. In combination with a more evenly force distribution, this means CC fixation might still be more effective than PS fixation in osteoporotic bone. [70]

CC fixation might be more effective than PS fixation as the risk of ALVFs is probably smaller in CC fixation than in PS fixation due to more uniform stress sharing and thus less stress on adjacent levels. Furthermore, blood loss is similar in PS and CC fixation. CC fixation has not been researched yet in humans so even though it is considered a safe technique by Cusick et al., the safety of this procedure must be questioned before implementing it in humans. Nothing can be said about invasiveness and durability yet, as the research has been executed on only human cadaver spinal columns. Although CC fixation would be considered a safe and effective technique, it may appear relatively complex because of the surgical techniques involved. However, CC fixation is similar to PS fixation when it comes to universality, operation time and cost implementation. [70]

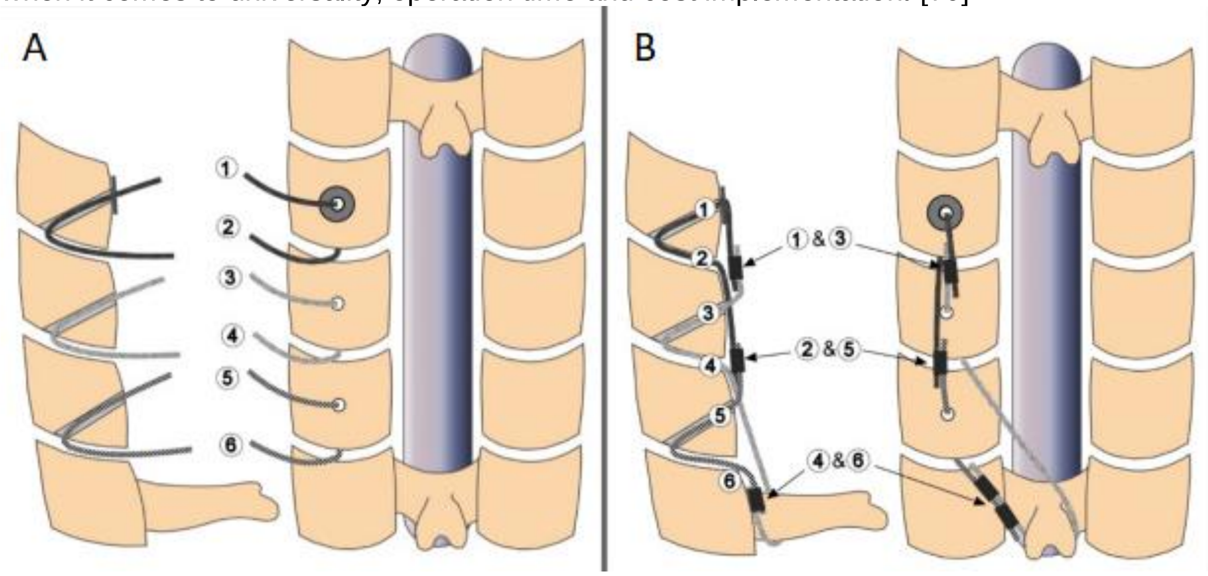

Figure 3: Unilateral wiring in CC fixation shown with corresponding numbers. The placing of the wires (A) and the connections of the wires (B) are shown. Spinous processes are removed in this figure, which is not required in the case of osteoporosis. [70]

6.1.2 Sublaminar wiring and spinal loop rectangle

Another fixation technique that includes wiring is sublaminar wiring (SLW), which is currently used in the treatment of scoliosis. Using SLW, vertebrae can be attached to a rod along the vertebral column. The newest shape of this rod is the Hartshill rectangle, also spinal loop rectangle (SLR). [71] This SLR is an oval, stainless steel loop. [72] To insert the wires, an incision has to be made along the vertebrae that will be fixated. After incision, paraspinal muscles are lifted and pulled back bilaterally from the spinous processes, laminae and pars interarticularis, up to the tip of the transverse processes. In addition to creating light for wiring, this helps preparing a good fusion bed for bone grafting. [71]

To use SLW, midline posterior exposure up to the transverse processes has to be realized. The sublaminar spaces are created by cutting the interspinous ligaments and midline ligamentum flavum. After exposing the sublaminar spaces, 20 gauge stainless steel double looped wires are passed at each level in cranial direction, as seen in figure 4. The wire is then cut through. The size of the SLR required must then be measured to choose the proper size to create optimal sagittal balance. The wires are passed through the SLR with the cranial wire ending inside the SLR and the caudal wire ending outside the SLR at each level. At the lower end of the SLR, this is reversed to prevent down slide of the SLR. [71][72] After final tightening, the extra length of wire is cut and buried on itself over the lamina. [71] Finally, the sublaminar spaces are packed with gel foam and graft bed preparation for posterior fusion is done. [72] For thoracolumbar OVCFs, stabilization of three or four levels cranial and three levels caudal to the fractured vertebra has been shown to be optimal, according to Patil et al. [71]

Patil et al. have done research on SLW with an SLR in osteoporotic vertebrae. In this research, the duration of surgery was ranging from 120 to 230 minutes. Blood loss was ranging from 150 to 2000 mL. [71] Cheng et al. found a blood loss of 824 +/- 440 mL in comparison with a blood loss of 1791 +/- 816 mL in open back PS fixation. [57] The fact that an open back surgery for multiple levels is needed ensures high invasiveness. After implanting SLW with an SLR, the average VAS score has been found to be decreased from 8.98 to 2.76. Single level wire breakages and implant backouts were seen in 14% of the patients, but these were all clinically asymptomatic. The patients in whom this occurred all had continued smoking and had not continued regular antiosteoporotic treatment against other instructions. 40% of all patients had a significant neurologic deficit after surgery, due to epidural cord compression caused by the sublaminar wires. 90% of these patients improved completely after an emergency surgery, [71] but the remaining neurologic deficits and the amount of emergency surgeries needed remain very undesirable.

SLW with an SLR is semi rigid and not only strong enough to hold the spine in normal alignment, but also allowing controlled axial, anterior column collapse to happen. Because of this, the system should not fail, where PS fixation might. In 7% of all cases, failure of fixation occurs in SLW with an SLR. [73] SLW with an SLR relies on the lamina for its hold, which is one of the strongest parts of an osteoporotic vertebra. [71]

The easy learning curve, user-friendliness and safe implantation technique, make this a viable alternative option for stabilizing OVCFs. [71] Because of the different sizes of the SLR available, this is a universal technique. In research of Cheng et al. it turned out that the costs of a construction with sublaminar wiring are much lower than a construction with pedicle screws, respectively $8,341 (16.0 fixation points) and $13,462 (17.1 fixation points). [57]

In research of Bhojrai et al. 17% of all patients (6 out of 36) had breakage of sublaminar wires at the lower end of the construction after an average follow-up of 6.5 years. None of the patients had SLR breakage. This suggests that the durability of SLW is not as long as desirable, despite not giving clinical complications. The incidence of ALVF was 19,4% of patients (7 out of 36). According to Bhojrai et al., no grave neurological complications were encountered, even in congenital deformities. The adverse events related to wiring are therefore comparable to any other system and are a consequence of improper technique. [72]

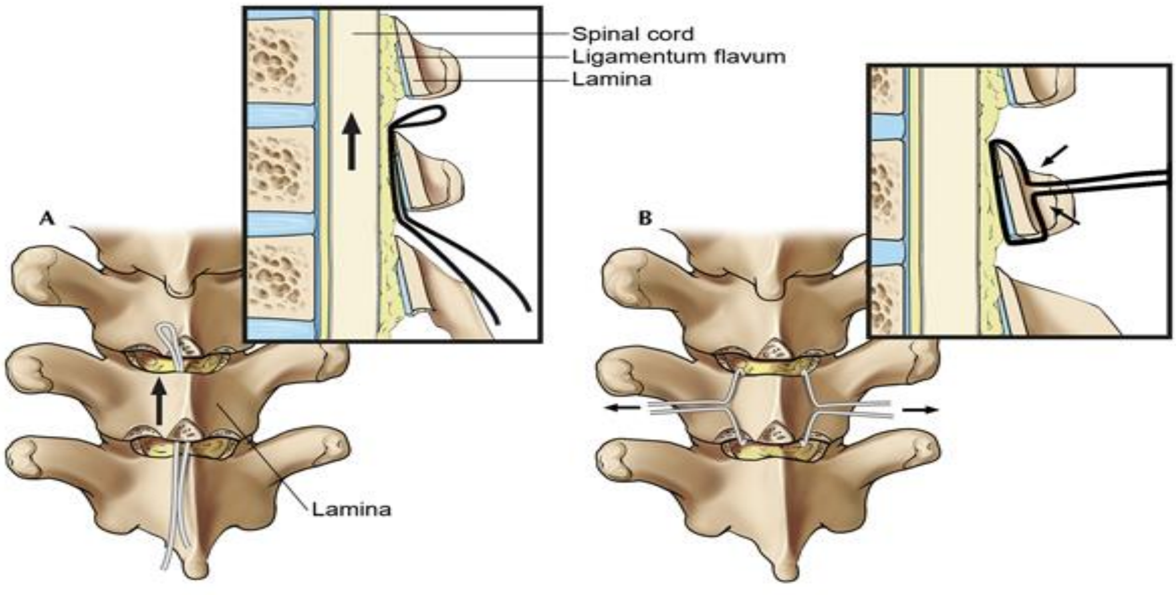

Figure 4: Sublaminar wiring. Wires are passed through the sublaminar spaces, namely between the spinal cord on one side and the lamina and ligamentum flavum on the other side (A). Thereafter, the wire loop is pinched over the lamina, so that ventral protrusion into the spinal canal is avoided, and cut to allow the use of each half of the wire on one side of the midline (B). [107]

6.2 3D-printing

It has already been proven it is possible to create an exact replica of a vertebra with 3D printing, using only PET/CT data. The data was interpolated, segmented, filtered, converted to binary volume and ultimately printed. When measured and compared to the scanned vertebra, the printed vertebra proved to be the same as the original. [74] A titanium replica for T9 has already been used after resection of the concerning vertebra due to a tumor. The implant had porous end plate morphology, which assists in osseointegration, and was designed with fixation holes for pedicle screws. To insert the implant, a sagittal incision was made from vertebrae T6 to T12 and a lateral incision to reveal the bilateral joints of vertebrae T9 and T10. Vertebrae T6 to T12 were fixated using standard pedicle-fixation techniques. Subsequently, vertebra T9 was removed, while maintaining the vertebral discs. Next, the implant was inserted and connected to the rods with pedicle screws. [75] Xu et al. presented a case report about the implant of a C2 prosthesis. This time, the vertebral discs were removed, and the caudal side of C1 and cranial side of C3 were removed for optimal surface area. [76] Both cases did not report on how they handled the spinal cord, but it is probable the posterior side of the spinal cord is not covered by the implant.

Implanting a 3D printed vertebra has only been done a few times, so the complication and mortality rates are still unknown. The treatment is rather radical and has a great impact on the patient. Therefore, it seems drastic to perform this transplantation on a patient with OVCF because these patients are often aged. However, an implant will not break again, will give enough stability and can be used for all patients since it is 3D printed. It will probably last long, but is not very user-friendly, since it is a fairly extensive surgery. In addition, because of the highly specialized equipment needed, it is rather expensive. An 'off-the-shelf' prosthesis is a more economical solution in most cases. [75]

Another application of 3D printing regarding osteoporotic vertebrae, is a 3D printed guide plate for PS fixation. For this, CT scans have to be reconstructed in 3D. The surgery is identical to regular PS fixation, but the difference is the guide plate, which makes sure the screws are positioned right and directed in the right angle. The use of this guide plate can reduce the operation time, fluoroscopy times and the amount of hemorrhage. [58] Acceptable placement rates vary from 90.6% to 100% [58][77] This method is just like the original, only more expensive. [58] A disadvantage of using this guide plate is the inability to perform the surgery percutaneously, so an open back surgery has to be performed.

6.3 Stem cells

Most methods only treat the actual fracture. With mesenchymal stem cells (MSCs) injected systemically, it is possible to treat the underlying condition and reach all sites that need repairing. However, a solution then has to be found for homing, differentiation and engrafting of the MSCs at bone sites, despite MSCs preferentially migrating to injury sites. [78][79] It is also possible to inject MSCs locally, only the actual fracture is treated then. [78]
To stimulate bone growth, MSCs should differentiate into osteoblasts. In case of osteoporosis due to aging, the amount of bone marrow MSCs is decreased, as well as the function of these MSCs. When MSCs are transplanted into bone, these will differentiate and stimulate bone growth. [78]

Parathyroid hormone (PTH) is shown to induce fracture repair by stimulating MSCs. However, in the case of osteoporosis, stem cells are not working as they should. Therefore, a study to the combination of PTH and systemically administered MSCs has been conducted. PTH enhances MSCs to migrate to the lumbar region. The therapy had promising results on rats and osteoporotic porcupine models, which could mean this would be helpful for patients as well, when allogeneic MSCs are appropriate for bone regeneration. [79] However, PTH has a limited duration of use, namely 2 years, after which only the use of bone resorption inhibiting drugs should be continued. [78] The durability of this newly formed bone is still unknown. The contribution of MSCs was evident, since both in vivo imaging and IHF analysis showed significant populations of cells in and nearby the defect, where they differentiated into bone-forming cells. [79] Therefore, it could be an effective method. However, due to only being tested in rats and, with large excess of PTH, in porcupine models, it is not yet safe for humans. Among others, the lack of axial weight bearing has yet to be researched. It is a universal, non-invasive and user-friendly treatment, because it consists of injections only.

Another option is to derive stem cells from adipose tissue, namely human perivascular stem cells (hPSCs). Compared to bone marrow MSCs, hPSCs are large in number, easily isolated and produce large cell yields. [78] These cells are tested locally in osteoporotic rats, in combination with NELL-1, an osteogenic protein. It showed no difference between hPSCs from osteoporotic and non-osteoporotic donors. Despite the dosage needing to be higher to obtain spinal fusion in rats with osteoporosis than in non-osteoporotic rats, the fusion rate became 83.3%. When researched further, this could be a valid method. [80] It seems an effective and safe treatment in rats, but more research has to be done before this could be implemented in humans. The durability of this treatment is also still unclear. Since the same method is used to inject hPSCs as MSCs, this is also a universal, non-invasive and user-friendly treatment.

Despite induced pluripotent stem cells being costly, several methods are being developed to reduce these costs. [81] The exact costs of MSCs and hPSCs could not be found, so it will be assumed these are also expensive.

6.4 Radiofrequency-targeted vertebral augmentation

Radiofrequency-targeted vertebral augmentation (RF-TVA) is a new vertebral augmentation system. It has been approved as treatment for OVCFs in Germany since 2009. It uses a small osteotome to create paths in the vertebral body to make targeted cavities in order to preserve more of the original bone. [82] RF-TVA is used in combination with ultrahigh viscosity PMMA (UHV-PMMA), which fills the targeted cavities and is hardened by radiofrequency. [33] UHV-PMMA is proven to be as effective as normal PMMA, but with a lower leakage rate. [82][83]

Most of the time, a unipedicular approach is sufficient, but in approximately 14% of the cases a bipedicular approach is necessary due to sclerotic bone. BKP, on the contrary, always needs a bipedicular approach. [82] RF-TVA shows a similar pain reduction as VP, lower PMMA leakage rate and a greater restore of vertebral height. Erdem et al. conducted a study on safety and effectiveness of RF-TVA, in which they found a 0,5% leakage rate. ALVF incidence in RF-TVA is unknown, since the method is relatively new. The method is effective and has a low complication rate compared to VP or BKP. [33][82] Georgy et al. and Bornemann et al. present a leakage rate of respectively 5% and 9,4%, in comparison with a leakage rate of respectively 12% and 24% when using BKP. [34][35] In comparison with BKP, little PMMA is needed and a great restorage of height is obtained. It is also proved RF-TVA is a significantly shorter procedure, [35] even when BKP was performed by two surgeons simultaneously. [82] RF-TVA can be performed safely with convenience for the surgeon, even after minimal training. [67] RF-TVA is more cost efficient than BKP, especially when treating multiple levels due to only needing one surgical set for up to three vertebrae. [82] There is no telling how long this method will last, but probably as long as VP, since the same material is used. Additionally, this method is universal, except for patients with active infection, cement allergy and coagulation disorders, just like VP and BKP. [31]

6.5 Alternative materials for PMMA

The disadvantages of PMMA, as described earlier, make researchers look for other materials that might be better than PMMA, such as UHV-PMMA, described under RF-TVA, and calcium phosphate (CaP) based bone cements. CaP is especially desirable in younger patients, because PMMA does not accommodate for remodeling, whereas CaP does. Several concepts have been developed that optimize CaP for minimally invasive application. The major limitations of this type of bone cements in load bearing situations are the brittle nature of CaP cements and the low tensile strength compared to bone. [84]

An example of a novel CaP based material is calcium sulfate hemihydrate (CSH) in combination with acetalized polyvinyl alcohol porous material (APVA-PM), which is an expandable bone cement. CSH is gradually converted into calcium sulfate dihydrate when mixed with water. This material can expand and does not produce heat during the setting process. In addition, it has a great biocompatibility and promotes bone healing without inducing inflammation. It forms a porous structure, which is excellent for the growth of new bone. By adding APVA-PM, the expansion, structure, mechanical properties and injectability are controlled. [85] It appears to be a good replacement, though it is not used in vivo yet and the complication rate is therefore still unknown.

Another example is strontium-containing calcium phosphate (Sr CaP) bone cement. The addition of strontium causes a stimulation of bone formation and an inhibition of osteoclastic bone resorption, which makes it an effective strategy for providing osteoinductive activity. This has already been applied in a cadaver, but not yet in living humans, so the safety of this procedure has to be questioned. The compressive strength of this strontium-containing CaP still falls in range with other CaP cements that have been used in VP or BKP. In the cadaver, no leakage has been observed. [84] This cement has not been tested in vivo yet, so nothing can be said about safety or effectiveness.

Both CSH and Sr CaP work the same as PMMA, so the usability, impact and universality are similar to current methods. The costs and durability are unknown.

6.6 Discussion and conclusion

In table 2, the grades given to the stabilization and fixation methods in development are shown. A PS system and VBS got a 6.3 and 6.9, respectively. The highest grades were given to stem cells, namely an 8.4 and an 8.1 for the different types. If stem cells are truly safe and effective, they could replace the use of a PS system and VBS, since they could provide a systemic treatment. However, the stem cells are not ready yet to implement in humans as it has only been tested in animals. [80] The grades for safety and effectiveness of stem cells have been based on those in rats and it thus has to be researched if this applies to humans as well. If the safety and effectiveness in humans are similar to those in rats, the use of stem cells in the treatment of OVCFs could offer a large improvement.

Looking at fixation of several vertebrae, no method in development has gotten a higher grade than a PS system. Since the PS system only got a 6.3, this means there is still a lot of room for improvement.

When it comes to stabilization of the vertebral body, RF-TVA has gotten the highest grade, namely a 7.4. In comparison with VBS, which is the current method and got a 6.9, RF-TVA could be a good replacement for VBS. Because VBS is currently combined with a PS system, RF-TVA should probably also be combined with this.

Table 2: The methods with respect to the requirements

	Safety (4x)	Effectiveness (4x)	Invasiveness (3x)	Durability (2x)	User-friendliness (2x)	Affordability (2x)	Universality (1x)	Average
VP	5.7	5.7	8.3	8.3	8.0	7.0	7.3	**6.9**
BKP	6.0	5.8	8.0	8.3	7.8	6.3	7.3	**6.9**
PS	6.0	6.2	7.0	6.0	6.5	5.7	6.7	**6.3**
VBS	6.0	5.8	8.0	8.3	7.8	6.3	7.3	**6.9**
Wiring								
CC fixation	6.7	6.3	4.3	6.8	5.0	5.7	6.5	**5.9**
SLW and SLR	6.7	6.3	4.7	6.8	5.3	5.8	7.0	**6.1**
3D printing								
Vertebra	4.0	8.0	2.0	8.7	2.7	3.7	9.2	**5.2**
Guide plate	6.3	6.3	4.7	6.0	7.2	6.7	6.7	**5.9**
Stem cells								
MSCs and PTH	8.3	9.3	9.7	8.0	10	3.3	9.5	**8.4**
hPSCs and NELL-1	8.3	8.5	9.7	8.0	9.3	3.3	9.5	**8.1**
RF-TVA	6.8	6.8	8.3	8.3	7.7	7.3	7.7	**7.4**
Alternative materials for PMMA								
CSH and APVA-PM	5.8	5.8	8.0	8.0	7.8	6.8	7.3	**6.9**
Sr CaP	5.8	5.8	8.0	8.0	7.8	6.8	7.3	**6.9**

7 Methods obtained by brainstorming

What could new ideas, including improvements of the methods found in subquestion 2, retrieved from brainstorm-sessions, look like and which of these is or are best?

Several ideas have been come up with, that might help in stabilizing OVCFs and fixating the vertebrae, from 3D printed molds to magnets. How these ideas could work, or why they would not work, is described below. A vertebra has to withstand an axial compressive force of 1.600 N, [86] but it is still unclear what additional strength is needed to stabilize the vertebrae and thus if the techniques described below are strong enough.

7.1 Fixation

Several ideas have been thought of when it comes to fixation of the vertebrae. This means the vertebra with OVCF is fixated to the adjacent vertebrae.

7.1.1 Blind rivet

A possibility to fixate a rod to the vertebrae is by using a blind rivet. A transpedicular hole has to be drilled in the vertebra, at the same location a PS is placed. A blind rivet with mandrel can be placed in the hole. The mandrel is then withdrawn, causing the blind rivet to get stuck as seen in figure 5. Instead of breaking off the mandrel, as is usual, this part can serve as a place for fixation of the blind rivet to the rod.

For this to work, the place of attachment has to be very strong. Since the pedicle is one of the strongest parts of an osteoporotic vertebra, it can be placed there. It is assumed the spongious bone will be easily compressed by the blind rivet, causing the blind rivet to attach to the cortical bone. The effectiveness of this should be researched further, but it will probably be similar to a PS system. A big disadvantage of this system is that it is very hard to remove and that it should be placed perfectly to the back of the vertebra to achieve the required strength.

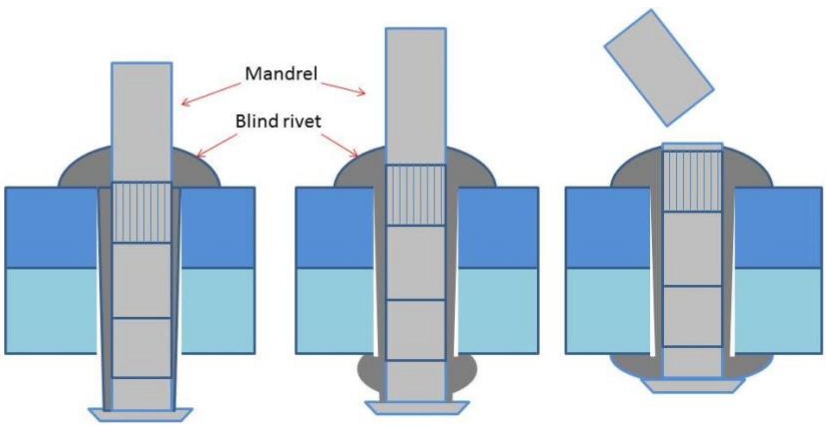

Figure 5: Installation of a blind rivet [108]

7.1.2 3D printed mold

3D printing has more and more applications in medicine nowadays, so this could be a possibility to fixate the vertebrae.

One way to use a 3D printed mold is by fixating three vertebrae to each other. Two kinds of molds have been thought of to fixate the spinous processes to one another. The first is a small strip that only covers the posterior side of the spinous processes. This is seen in figure 6A. This will have to be attached in a posterior approach. Since the spinous processes have a specific form, it is probably not possible to place a mold around it in one piece. Therefore, different pieces would have to be attached to each other on the most posterior side of the spinous processes. The second kind of mold is a mold completely around the spinous processes. This idea is shown in figure 6B. This will have to be attached in a bilateral approach in which two half parts of the mold are attached to one another on the posterior side of the vertebrae.

The biggest advantage of these ideas is the universality of them. Since the molds will be 3D printed, the method would be available for everyone. However, when applied, breakage of the spinous processes could occur. Also, the question is raised whether a 3D printed mold would be strong enough. For instance, a strong material like metal can be used, but a 3D printer that can process metal is very expensive. [87] However, the acquisition costs are only once, after which a lot of patients could be helped by the use of this device. When this material is used, the strength is still not guaranteed and should therefore be researched. The molds could also be made by moulding a material into the right shape during surgery. The material should have hardened before finishing the surgery, since otherwise the material can deform or cause migration of the material. If a material hardens before finishing the surgery, it would be either not moldable enough to place or a long time would have to be waited during surgery.

Both 3D printed molds could be used in combination with CC fixation. If a 3D printed mold is made with protrusions with holes in them, the wires used in CC fixation can be passed through those holes as well as through the facet joints. This ensures fixation of the facet joints as well as the spinous processes. By using this combination, it is ensured the mold will stay in place and the instability usually remaining after using wiring could be overcome. This way, total stability of the OVCF with its adjacent vertebrae could be accomplished. However, the procedure is not user-friendly as it probably is complex to implement.

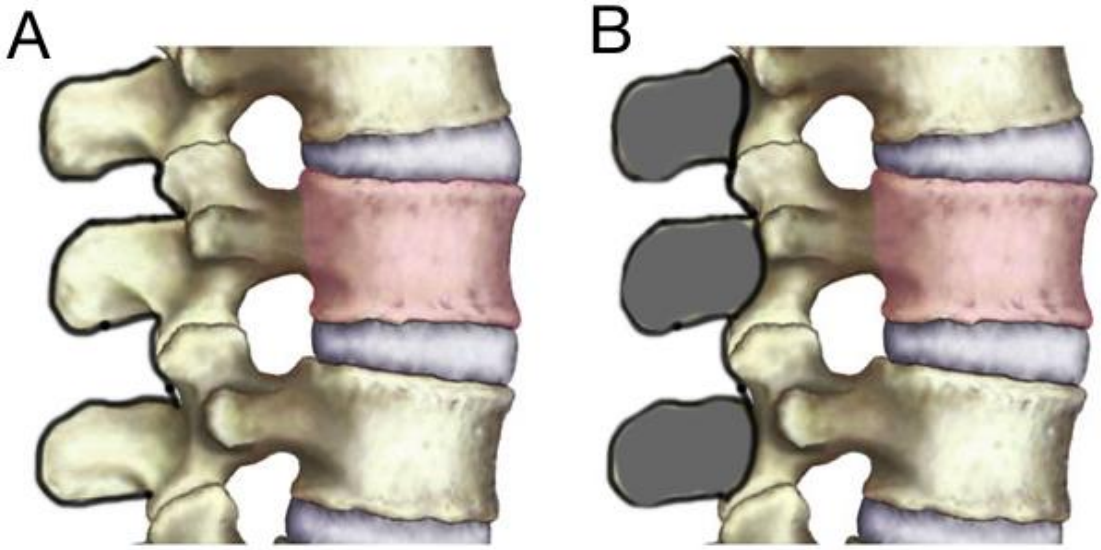

Figure 6: A mold posterior of the spinous processes (A) and around the spinous processes (B) are shown.

7.1.3 Silicone cover

Another idea thought of could be done with silicone around the spinous processes and a rigid plate or little rods between them. In this way, the spinous processes are covered in silicone and fixated to one another. Since it is elastic, it should fit everyone if the right size is chosen. This looks like a suitable solution, but the surgery will probably be very invasive, since the silicone has to be fitted around the spinous processes. Furthermore, a risk of rupture of the silicones or breakage of the spinous processes exists, when enough force is applied.

7.1.4 Magnets

The idea of using magnets to fixate the vertebra arose. An option would be to laparoscopically insert small magnets into the vertebral bodies. These magnets will attract each other and can thus stabilize the vertebrae. This idea is shown in figure 7.

Probably, extremely strong or large magnets are needed to acquire the required strength. For example, neodymium magnets are rather strong for their weight [88] and are biocompatible. [89] The use of magnets will not be applicable in a patient, because of limited space in the vertebral body and because it is not safe for a person to be magnetic. Another disadvantage is that it is unclear whether the vertebral bodies can withstand the attractive forces of the magnets. Even though the magnets keep the vertebrae vertical with respect to each other, they also attract each other between the vertebral bodies. The fractured vertebra is thereby even more pressured, instead of the pressure being divided over the surrounding vertebrae. The weight of the magnets should also be taken into account. Furthermore, it should be researched whether magnets dissolve and thus disperse particles.

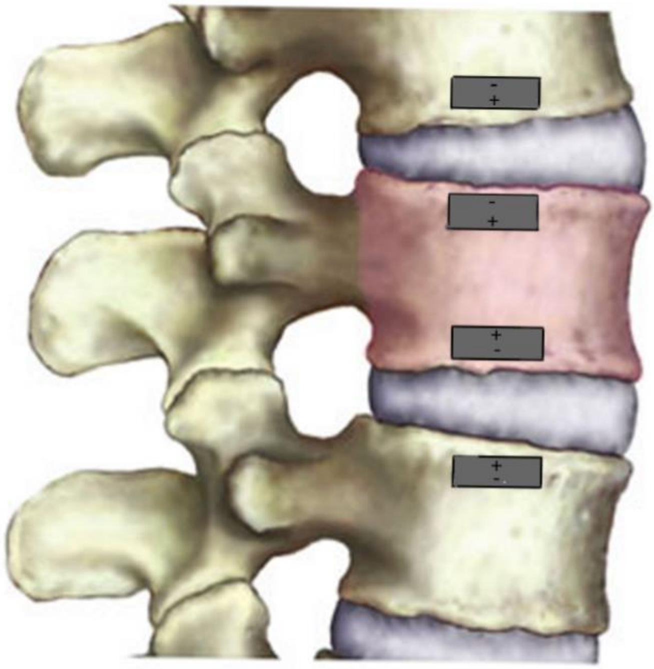

Figure 7: Magnets in the vertebral body

The use of magnets could be combined with inserting PMMA or one of the alternative materials in the vertebrae that contain magnets. In this way, not only the OVCF will be stabilized but also the adjacent vertebrae. Questions raised for this methods are whether the magnets would still work when they are surrounded by cement and whether they will be strong enough to stabilize the vertebrae. A disadvantage of this idea is that instead of in one vertebra, PMMA is needed in three vertebrae. The disadvantages mentioned for magnets also apply here.

7.1.5 Rollable plate

The next possibility is a rollable plate with a beam attached to it, which can be brought into the vertebral body through a drilled hole. In the vertebra, the plate is then rolled out, which gives the beam pull resistance, so it cannot be pulled out. This should be done in all the vertebrae that need fixation. All these beams can be attached to a large rod at the back of the vertebrae. This is drawn in figure 8.

There are multiple problems to this design. Because one side of the plate will still be big, inserting the plate will be a problem, as well as rolling the plate. When a material is rollable, it is probably not as strong as desired. Furthermore, the attachment of the beam to the plate is probably weak. Another problem is that the plate could move within the vertebral body when transverse forces are applied on the plate and thus destroy what is left of the cancellous bone. The idea of attaching something on the inside of the vertebral body could work, but should be done in a different way.

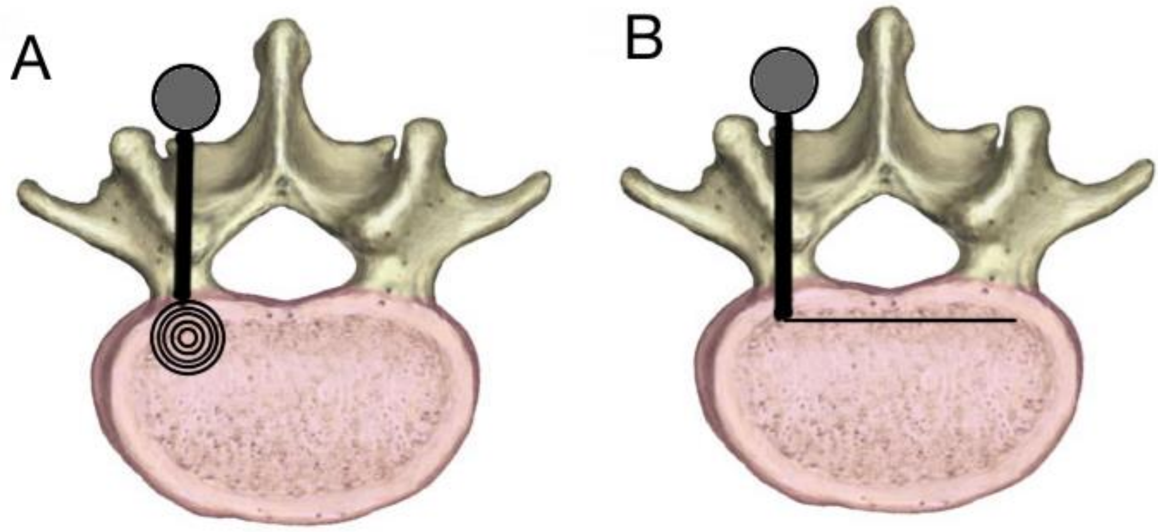

Figure 8: The rollable plate is shown rolled up (A) and rolled out (B). The plate is attached to a rod on the side where it is inserted.

7.1.6 Clamps

Fixation with staples was suggested, but after brainstorming it was concluded that clamps would work better. Clamps are u-shaped fasteners with sharp ends. While the clamp is fastened, the legs are pressed slightly towards each other. This ensures that the clamp will firmly attach to the material, since it wants to expand. In case of OVCFs, clamps can be used to fixate a rod to the vertebrae. It is a challenge to attach this to a rod, but this could be done by making one big clamp, with one leg in both pedicles. The posterior side of the clamp should be between the spinous processes, so no inconvenience is caused. There should be a rod on both sides of the spinous processes. These rods could be made with a hole where the clamp would be inserted through. A sketch of this idea is given in figure 9. A disadvantage of this system is the invasiveness and the strength needed for insertion of the clamp. Furthermore, it is unknown whether the clamp has enough friction in the vertebral body to stay attached and whether it is resistant to vertical forces.

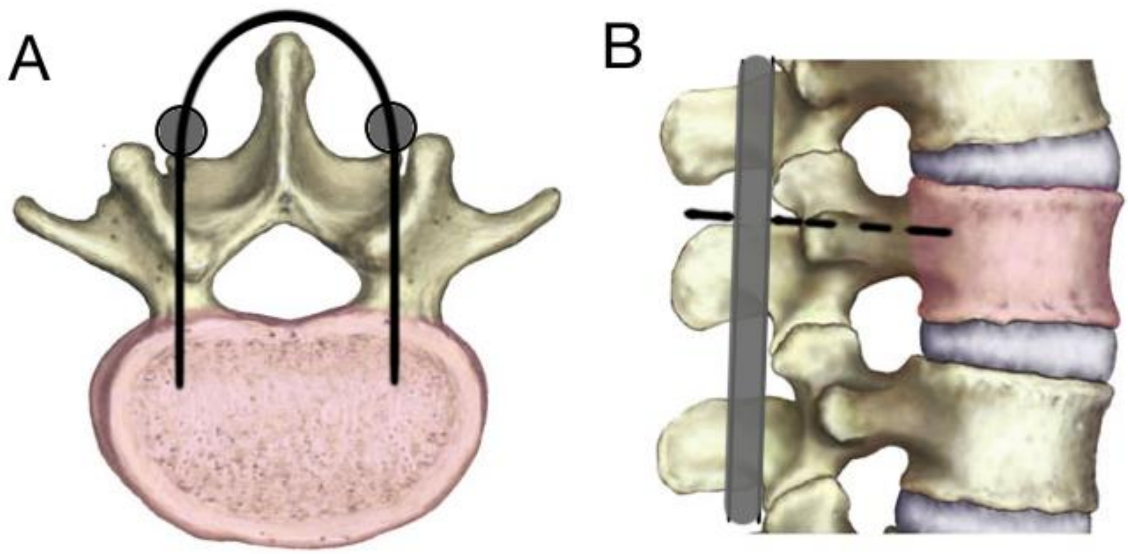

Figure 9: The clamp connected tot he rods is shown in a superior view (A) and in a lateral view (B).

7.1.7 Band or straps around the vertebrae

To secure the vertebrae, it is a possibility to wrap straps or a band around the vertebrae and attach these to rods at the posterior end of the vertebrae. Our vision of this idea is shown in figure 10. To prevent migration of the rods, it might be a more suitable option to guide the band or straps through or one more time around the rod. This will successfully stabilize the vertebrae, but will be very invasive and difficult to apply. Therefore, this idea is currently not viable.

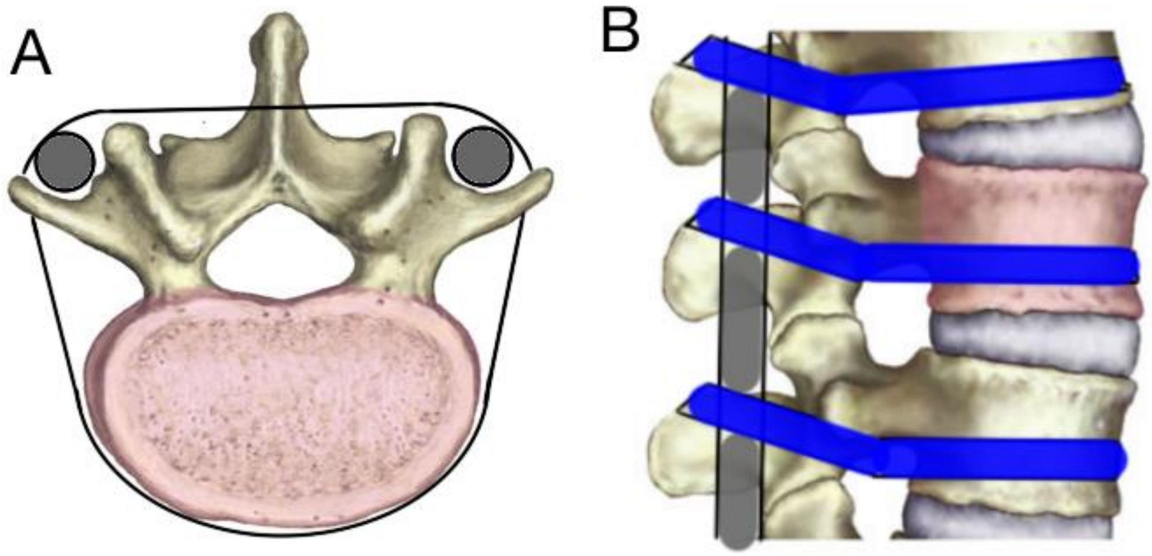

Figure 10: A strap around the vertebra while attaching rods in a superior view (A) and a lateral view (B).

7.1.8 Band around spinous processes

To take the load off of the vertebral bodies, the idea occurred to fasten the spinous processes with some sort of stiff, elastic band. In this way, flexion is restricted in this area, thus moving the gravitational forces from the vertebral body to the facet joints. The vertebral body could be spared like that. Instead of shifting the pressure from the vertebral body to the facet joints, it could also shift to the posterior of the vertebral body, which could lead to a new fracture. Another problem is finding a material strong enough, while still flexible enough to place it around the spinous processes.

A similar idea, interspinous implants, or bumpers, are already in use for spinal stenosis. Such a bumper is initially used to push the vertebrae from each other, instead of keeping them together. However, when a strong enough material for the strap around the spinous processes is used, it should also be able to hold them together.

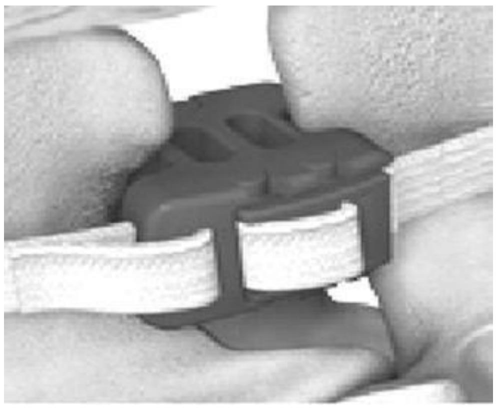

Figure 11: An interspinous blocker with woven Dacron around the spinous processes [90]

The second generation of Wallis is an interspinous blocker of polyetheretherketone, with woven Dacron around the spinous process, [90] as seen in figure 11. Several different versions of these interspinous implants are used, with the aim of unloading the facet joints, restoring foraminal height and providing stability, while still allowing motion. [91] The interspinous blocker displaces the loading dorsally, and thus reduces the load on the disc and facet joint. In degenerative spinal stenosis, spondylolisthesis and loss of segmental lordosis, this method has shown to reduce adjacent segment diseases, among which ALVFs. However, osteoporosis is a contraindication for an interspinous implant. [90] Furthermore, it has a complication rate of 11.6-38%, reoperation rate of 4.6-85% and a 66.7-77% frequency of poor outcomes.

Additionally, the costs were $17,600 for one-level procedures and $57,201 for three-level procedures, not considering operation and recovery room costs. [92]

7.1.9 CC fixation with an SLR
Instead of combining an SLR with SLW, an SLR also could be combined with CC fixation (CC-SLR). The wires used in CC fixation can be passed through the SLR before attaching them to each other. This will fixate the SLR in its correct place while fixating the facet joints at the same time, hereby avoiding the neurologic deficits caused by SLW.

7.1.10 Barbs
Instead of a screw in a PS system, a pin with barbs can be used to prevent pull-out. This idea is similar to a screw, but a screw will probably be better fixated because the barbs leave gaps when inserted in a rigid material, like osteoporotic bone. In a somewhat elastic material, this would probably work great. To solve this, instead of inserting PMMA, an elastic material can be used, but this will probably give the same complications as the use of PMMA in PS systems. Besides, instead of a smooth pin, the screw has screw thread for more friction. An idea is to let the barbs expand, but this is similar to and has no visible benefit over expandable screws.

7.2 Stabilization
Different ideas have been thought of to stabilize the fractured vertebra from inside the vertebral body. When the spongious bone in the vertebral body is compressed, a structure can be brought in, which supports the cortical bone at the superior and inferior side of the vertebral body. In this way, almost the whole vertebral body is filled, which prevents collapse. Several options for such structures are discussed below.

7.2.1 Foldable structure
An option is using a foldable structure, like a stent, to hold up the vertebral body instead of using it in combination with PMMA. A stent is designed to withstand interior force instead of exterior force though. What would make a foldable structure able to withstand greater forces, is using a spherical shape instead of a cylindrical one. A sphere is proven to be about 40 times stronger than a cylinder. [93] The problem is how to fasten the sphere firmly once expanded. An idea to do this, is shown in figure 12. The material used should be rather strong, because it has to withstand great forces while it is not a massive structure. To improve the strength of a secured sphere, the material could be made thicker than that of a stent. The difficulty is that the stent in folded form will then be bigger, which leads to a more invasive procedure. The structure in figure 12 will probably be strong when expanded, but it will be too large to insert. It seems impossible to make a small, insertable structure, which can withstand great forces when expanded at the same time. Moreover, when this structure could hold these forces, the upper or lower part of the vertebra probably can not since the pressure point is relatively small.

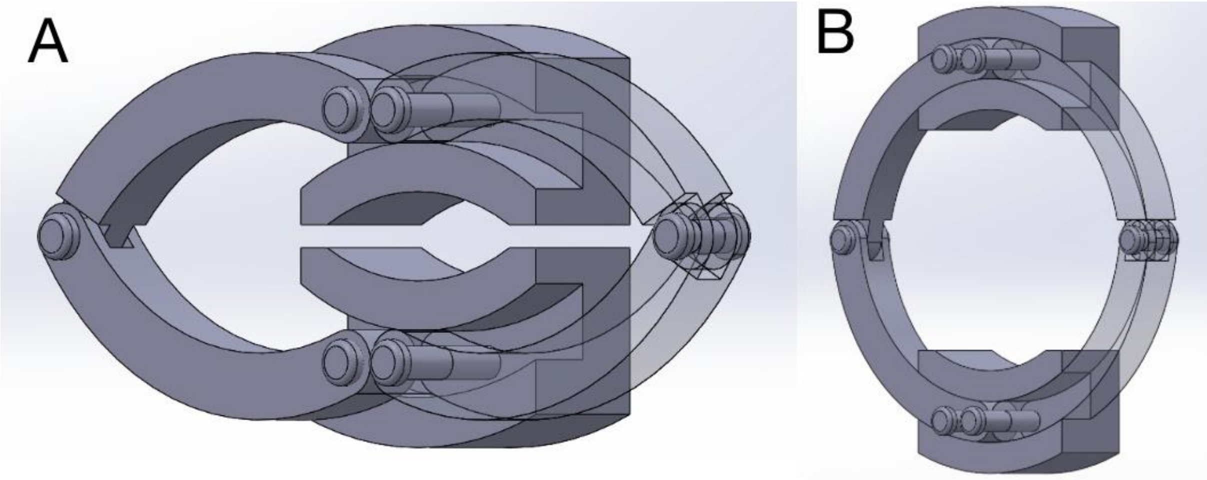

Figure 12: The structure is shown folded (A) and expanded and secured (B). It is secured with a block that is pushed into position by the use of springs, which, in this drawing, are at the back of the block.

7.2.2 Inflatable ball

A similar idea is to put an inflatable structure inside the vertebral body, which could then be inflated. In this way, the vertebral body will be stabilized. Inflatable structures are proven to be capable of being very strong. For instance, an inflatable dyke is used in the Netherlands. [94] An advantage of this is that it could be inserted through a small opening, which can be done minimally invasively. When multiple tetrahedrons are made inside this structure, this will distribute the forces more evenly.

7.2.3 Little cement balls in the vertebra

To prevent the leakage of PMMA into the spinal canal and the heat released during polymerization causing damage, the idea occurred of implanting the cement in set form, in many little pieces. To prevent these pieces from migrating, a cover should be placed around the pieces to keep them in place. This will hopefully stabilize the vertebrae, but the material of this cover should be carefully chosen to prevent undesirable interaction with surrounding tissue.

7.3 Options with multiple combination possibilities

Several combinations of methods have already been suggested, but some methods can be combined with multiple other methods. Stem cells, for example, could be combined with any other method. A combination of systemic stem cells with local treatment seems optimal, where the latter could be done with stem cells as well, or with one of the other options. Furthermore, all procedures that use PMMA can be combined with the use of alternative materials for PMMA, such as Sr CaP and CSH. A combination of an external fixation and stabilization and internal stabilization could also be made, an inflatable structure in combination with a 3D printed mold for example.

7.4 Discussion and conclusion

Based on the requirements, several ideas can be discarded. Since the complication and mortality rates are unknown, the safety will be assessed on the basis of the invasiveness, assuming a less invasive method is safer. The only method that can be excluded on the basis of safety is the use of magnets, since it is not safe for someone to be magnetic. The blind rivet is excluded by effectiveness, as well as barbs and a foldable structure. The rollable plate and the clamps can be written off due to effectiveness and invasiveness. The band or straps around the vertebrae can be ruled out on the basis of invasiveness and probably also on user-friendliness. The 3D printed molds and silicone cover should be discarded based on invasiveness. Since the band around the spinous processes appeared to be already in use and osteoporosis is a contraindication for this method, this idea is omitted. This leaves the combination of CC fixation and an SLR, the inflatable ball and the little cement balls in the vertebral body. Based on the requirements, these are the most viable options of the new ideas and will be further elaborated in chapter 8.

8 Concept models

What do concept models of the best fixation methods of subquestion 3 look like and to what extent do they meet the requirements?

As said before, CC-SLR, the inflatable ball and the little cement balls in the vertebrae are the most viable options for a new method of OVCFs. Among others, materials, insertion manner, operation procedure and expected complications of each method have been researched and are described below.

8.1 CC-SLR

As said before, CC fixation can be combined with an SLR to fixate the vertebrae. Figure 13 shows the way CC wires would secure the SLR. Three facet joints are fixated and thus two vertebrae are securely fastened. Using one wire in total was considered, but ultimately using one wire in each facet joint was chosen, so only one wire has to be replaced when it breaks and the implantation technique will be easier. This means wires 1 and 2, 3 and 4 and 5 and 6 are the same wires. The connective pieces of wires 1 and 3, 2 and 5 and 4 and 6 are not shown in figure 13, to clarify the image. The CC wires are passed around the SLR two or more times to prevent migration of the SLR. What could also be done to prevent migration is attaching wire 1 on the left to wire 3 on the right and wire 4 on the left could be attached to wire 6 on the right and vice versa. This way, wires would also be passed around the top and bottom of the SLR.

In both CC fixation and SLW, 20 gauge, stainless steel wires are used. [70][71] Therefore, CC fixation will ensure a similar attachment of the SLR as SLW. The SLR is, as described before, an oval, stainless steel loop. [72] CC-SLR could be more effective than PS fixation or one of both methods on itself, since Cusick et al. found CC fixation on itself to be as effective as a PS system. [70] An SLR can usually hold the spine in normal alignment and allow controlled axial, anterior column collapse to happen, [73] so a combination with CC could result in more strength and thus more effectiveness. However, it is a very rigid structure, so it could come loose easily or cause ALVFs.

A few problems occur in this idea. The surgery is either very invasive or very non-user-friendly. An invasive surgery would mean an easier implantation technique, but it is ought to be possible to perform this surgery minimally invasively. However, this ensures a very complex implantation technique, which is not possible yet. Because of the invasiveness of the procedure, it will probably have a significant revalidation time. In elderly, this revalidation time might be even longer and will thus have a greater impact on the patient. However, the relief of pain the patient would hopefully experience would compensate for the temporary convenience of revalidation.

The facet joints of elderly are often deformed, which makes it hard to determine the exact place to drill a hole for a wire minimally invasively. [Dr. M.C. Kruyt, personal communication, 06/12/2018] Since just CC fixation is a complicated method, [70] combining it with an SLR will be even more complicated. It will therefore take some time for surgeons to become familiar with this method. It will probably pay off over time though, since less serious complications are expected that could be an indication for reoperation, such as infection or system failure. A minimally invasive surgery should have the preference over a user-friendly one when possible, since invasiveness was given a higher weight in chapter 5.

The costs of the materials used in CC-SLR are ought to be similar to those of a PS system. Though, operation time would be longer and thus the overall costs higher than PS fixation when a minimally invasive manner is used, due to the complexity of the procedure. Complications that might occur are breaking of the wires, migration of the SLR and any of the general surgical and implantation risks, such as infection and bleeding. No additional complications of placing the SLR are expected since they would have come forward in an SLR in combination with SLW. However, complications due to CC fixation are still unknown and could thus still come to the surface. If clinical problems occur, the system would be difficult to remove, but not more difficult than removing a PS system.

The new method would probably last long enough since wire breakage usually does not give any clinical problems, even though breakage of wires is seen in 17% of all cases of SLW with an SLR [72] and is expected to be similar in CC-SLR. Therefore, this will probably not affect the effectiveness. Furthermore, this method does not have extensive exclusion criteria, so the universality of the system will not be an issue.

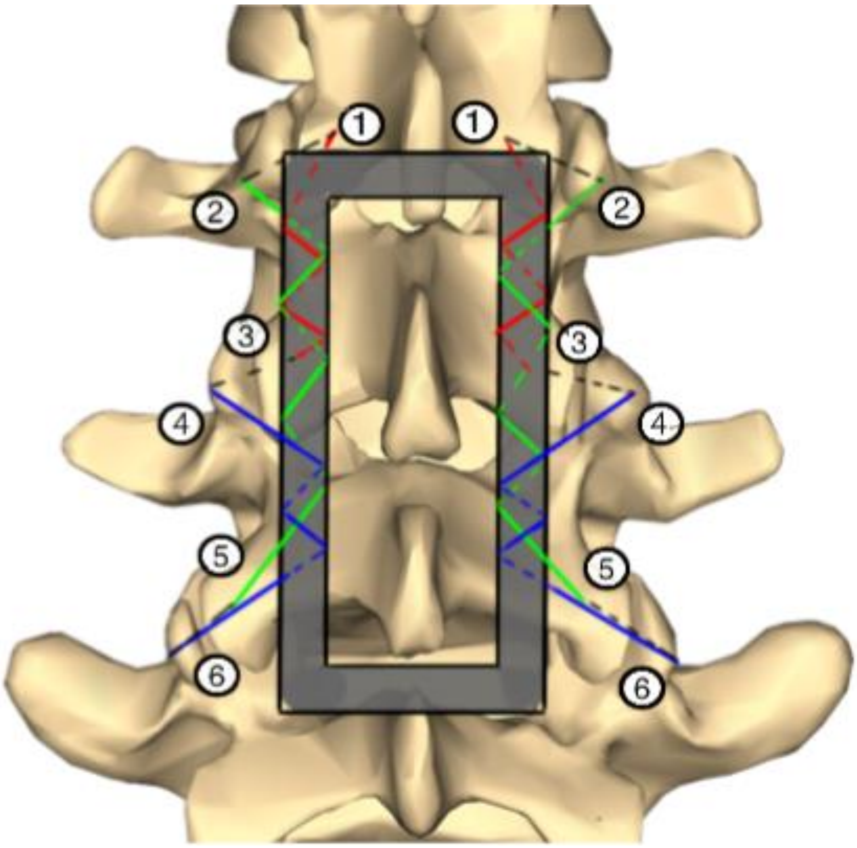

Figure 13: The SLR is shown fastened by wires of CC fixation. The red, green and blue lines represent wires 1 and 3, 2 and 5 and 4 and 6, respectively. In this image, the SLR is shown as a rectangle, but in reality it is an oval loop.

CC-SLR could be used in combination with a PS system with PMMA. This would ensure extra strength, and could prevent possible pull out or breaking of the wires because of double fastening, since the system is fastened in the facet joints, as well as in the pedicles. The PSs would be posteriorly attached to the SLR in the way they usually are attached to rods. The PSs should be placed first and the CC wires could then be passed above and beneath the PSs around the SLR, to prevent downslide of the SLR even more. It would be more expensive, due to the extra material and surgery time needed, so it has to be researched whether this system is more cost-effective with or without PSs.

8.2 Stabilization

CC-SLR could be combined with one of the two following internal stabilization techniques to ensure extra stabilization and restoration of vertebral height. One of these two could also be combined with a PS system.

8.2.1 Inflatable ball

As said before, an inflatable structure could be put inside the vertebral body, which could then be filled with water and stabilize the vertebral body this way. Water is chosen as filling material, because water is a harmless material in the off-chance the structure ruptures. Furthermore, a fluid divides the forces more evenly than air.

The material that is suitable for an inflatable structure, has to meet several requirements. It has to be biocompatible, strain resistant, elastic and impermeable for water and should not rupture under a pressure of at least 25 bar. [Dr. M.C. Kruyt, personal communication, 06/12/2018] To meet these requirements, a polymer would be best, since it can be designed to meet requirements and can be a strain resistant and elastic material. However, a disadvantage of the use of polymers is their low mechanical strength. Polymers with a glass transition temperature (Tg) lower than the body temperature, so a maximal Tg of 37ºC, are in an elastic state, so the most strain resistant, when implanted in the body. Optimally, the used polymer has a Tg of just below the body temperature since the material will then be in the strongest state, while still elastic. [95]

Many polymers are available so it is difficult to choose the correct one. Materials already in use in medical applications, such as sutures, could be applicable, as well as materials used for inflatables. For instance, poly(vinyl chloride) (PVC) and nylon are materials used for inflatables, but PVC and nylon have Tgs higher than the body temperature [96] so they will be in a glassy state once implanted in the body. Another option is poly(ethylene terephthalate) (PET), which is already used in several implants because of its mechanical properties and biocompatibility. Its antibacterial properties should be improved, for instance by the use of silver ions in the implant. [97] However, the Tg of PET is 72ºC and will therefore reach the glassy state after implantation. [96] Then, poly(propylene) (PP) was researched. It is currently used in sutures and meshes, and is biocompatible. [98] Furthermore, it has a Tg of -10ºC. [96] Therefore, the use of PP as material for this application is an option. Silicone rubber was then found. Normally, silicone rubber is rather permeable, [99] but at MIT, they were able to 3D print complex forms of silicone rubber, which can be programmed to inflate or deflate. [100] When the permeability is low enough to hold air inside, it should also be able to hold water inside. An example of silicone rubber is poly(dimethyl siloxane) (PDMS), which shows many positive characteristics, like elasticity [101] and strength. [102] Furthermore, PDMS has a Tg of -124ºC. [103] Moreover, PDMS has a sufficient biocompatibility and low manufacturing costs [104] Both PDMS and PP are possible materials for this application. However, not all materials available have been researched, and the materials researched are not researched extensively enough, so further research should be done. Combinations of polymers should also be researched.

When a hollow ball is used, the gravitational forces will compress the ball, which will want to expand to the sides, thus putting pressure on the sides of the vertebral body. To prevent this and distribute the forces more evenly, the inside of the ball should be made out of tetrahedrons from the same material as the ball, so they are also strain resistant. This concept is shown in figure 14. The ball can be closed in several ways, but the best option might be placing a valve at the end of the ball. This way, the ball can be filled up when it does empty over time.

The invasiveness of the inflatable ball is similar to that of VBS. The pressure gradient could easily be overcome if the water is inserted with a pressure high enough. Because of the valve, the water will remain inside the inflatable ball. Furthermore, BKP currently uses a balloon which also does not experience any problems with inflating in the vertebral body. [16] An expected complication is rupture of the ball, causing a leakage of water and possibly resulting in a refracture. General surgical and implantation risks, such as infection and bleeding, can also be expected.

Since surgeons are already familiar with the insertion method of BKP or VBS and this is very similar to the insertion method of the inflatable all, this will probably be a user-friendly method from the beginning. The costs of the inflatable ball will be lower than those of VBS, since neither PMMA or a stent are used in this application. Even though more of the material for the ball is used than in BKP, this will probably not affect the costs much, since the material is ought to be rather inexpensive. Questions were raised about the durability of the inflatable ball. Even though water would be able to distribute the forces more evenly, it is unknown whether the material of the ball will last long enough. The implant is, however, relatively easy to remove when complications occur.

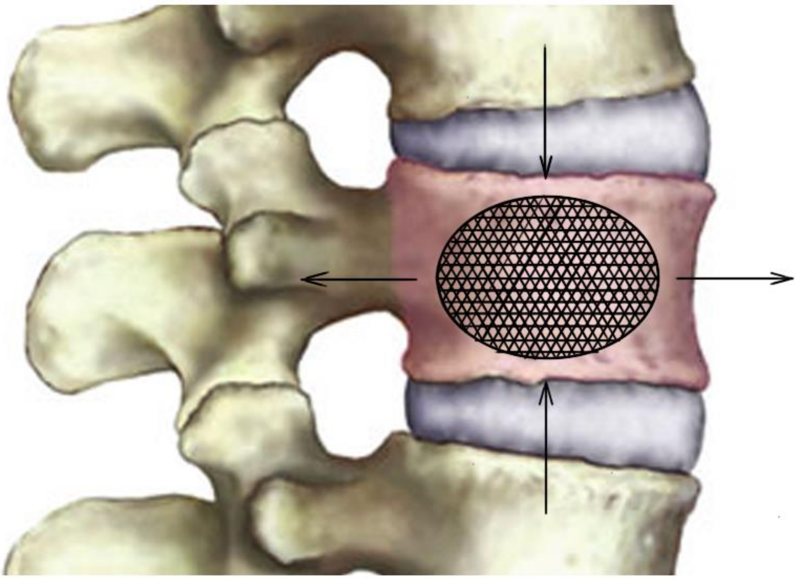

Figure 14: An inflatable ball with tetrahedrons inside is shown. The vertical forces are drawn, which cause the horizontal forces on the surroundings.

8.2.2 Little cement balls in the vertebral body

Instead of filling a ball with liquid, it could also be filled with something harder, like PMMA, which could withstand the forces more easily. To avoid the disadvantages of PMMA, little cement balls could be inserted. Because of the cement filling, the ball has to withstand less force than the inflatable ball, and could thus be made of thinner or weaker material. PP or silicone rubber like PDMS could be used, because the cover needs the same characteristics as the inflatable ball, but sometimes in a lesser degree, so more materials are available. For example, the material does not have to be as impermeable in this application. The cement will be made into little balls with a diameter of 2 to 3 mm, to prevent heating and ease the removal of cement when an infection occurs. First, a cavity has to be made by inflating the cover, after which the balls can be inserted through a slightly bigger working canal. This idea is shown in figure 15.

The invasiveness of the little cement balls in the vertebral body is similar to that of VBS, as well as the inflatable ball. Insertion of the little cement balls into the vertebral body will be a difficult procedure because a way for inserting the cement balls against the pressure gradient has to be found. It has been thought of to inflate the surrounding cover and slowly release pressure when the balls are being inserted into the cover. Also, the closing method of the cover has to be chosen wisely. Sutures have been thought of but the cover might rupture on this point. When the method is applied more often, surgeons will become familiar with it and the method will therefore be easier to apply.

The costs of the little cement balls will be similar to those of VBS, since approximately the same material is used. While no stent is needed in this application, the PMMA has to be formed in a specific shape outside of the body, which will make the costs similar. This method is considered to be able to last as long as VP and BKP, since it is mostly made of the same material. The cement balls are more difficult to remove than the inflatable ball but easier than VP or BKP.

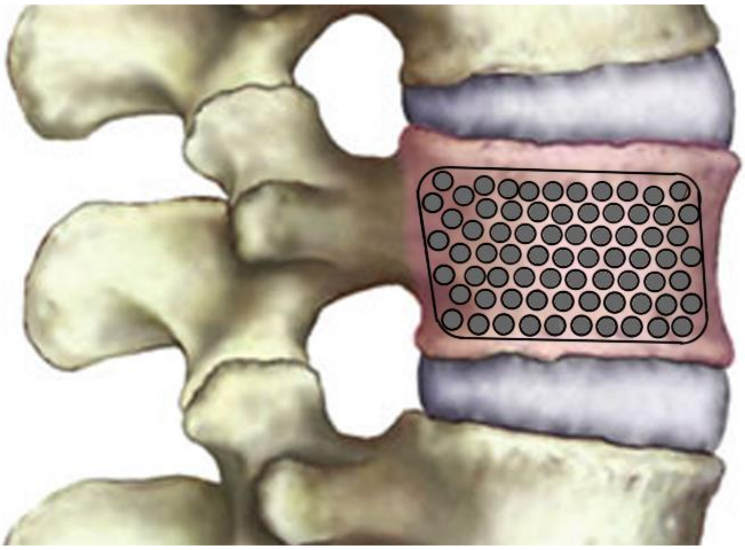

Figure 15: Vertebra filled with little cement balls with a flexible cover around them

8.3 Discussion and conclusion

As said before, a PS system and VBS get a 6.3 and a 6.9, respectively. Opposite to this are the grades given to the concept models, namely a 6.1, 6.1, 7.1 and 7.1 for CC-SLR, the combination of CC-SLR and PSs and an inflatable ball filled with liquid or little cement balls, respectively. These grades are shown in table 3.

According to the grades, the new methods for external fixation of the vertebrae would not be better than the current method. This is due to the high invasiveness and low user-friendliness of the procedure needed to implant CC-SLR. Apart from the grades for invasiveness and user-friendliness, CC-SLR scores higher than a PS system for every requirement. When the method would be changed to a less invasive procedure, this would mean it would become better than the current method. It might become an even less user-friendly procedure, but the invasiveness of the procedure weighs more, and is thus more important. Combining CC-SLR and PSs will be more effective and durable than just CC-SLR, since the system is secured even better and will thus not break as soon as CC-SLR. However, the safety of CC-SLR with PSs drops below CC-SLR, since the complications due to PMMA also occur. The user-friendliness and affordability also drop, since the surgery is more extensive.

When it comes to internal stabilization of the vertebral body, the new methods score higher than the current method. Even though the difference is not big, it still presents possibilities for internal stabilization. Currently, the method for internal stabilization is combined with a PS system, a method for external fixation. To achieve a better outcome, the inflatable ball filled with liquid or little cement balls should also be combined with a method for external fixation, whether this is with the new method or with one of the existing methods.

		Safety (4x)	Effectiveness (4x)	Invasiveness (3x)	Durability (2x)	User-friendliness (2x)	Affordability (2x)	Universality (1x)	Average
Current methods	**PS**	6.0	6.2	7.0	6.0	6.5	5.7	6.7	**6.3**
	VBS	6.0	5.8	8.0	8.3	7.8	6.3	7.3	**6.9**
Concept models	**CC-SLR**	6.7	7.0	4.3	6.8	4.7	6.0	6.8	**6.1**
	CC-SLR and PSs	6.0	7.8	4.3	7.4	4.4	5.1	6.9	**6.1**
	Inflatable ball	7.0	6.2	8.0	6.7	7.5	7.7	8.0	**7.1**
	Little cement balls in the vertebral body	6.8	6.2	8.0	7.3	7.7	7.0	8.0	**7.1**

Table 3: The current and new methods with respect to the requirements

9 Discussion

The applicability of the methods mentioned in chapter 8 to more patients than just our study population and the validity of this study are evaluated below. Furthermore, future research possibilities are described.

9.1 Validity

The tables in chapter 6 and 8 have been filled in based on research as much as possible, but the given grades remain subjective and might not correspond to reality since they were given by researchers with no experience in this line of field. Moreover, some grades had to be guessed, since not all data is known yet. A more objective way did not seem possible within the limited time and resources available. It would be more accurate to let medics or engineers, experienced in this line of field, fill in the table after reading the information about the methods in this study. This is a time consuming process, since medics have to read up on these methods to estimate a grade for them.

As said in chapter 7, the pressure on the vertebrae is known, but the pressure osteoporotic vertebrae can still withstand is unknown so the additional needed strength from the fixation technique is unknown. Therefore, it is difficult to assess whether the methods would be effective to treat OVCFs.

Since the ideas in chapter 7 and 8 are obtained by brainstorming, not all ideas possible have come up and improvements are still possible. Much research is still needed to draw an objective conclusion about these techniques. The ideas obtained in chapter 7 and 8 might work, but are also written to inspire others into finding new solutions for this age-old problem. Furthermore, in chapter 6, not all methods being developed are summed up, due to limited time. The most promising methods are described though. For example, many alternative materials for PMMA are available, which made it impossible to research all of them.

The original idea was to obtain the requirements in chapter 5 by brainstorming sessions and interviews with medics. Due to a lack of time, only one medic, namely dr. M.C. Kruyt, has been interviewed. This means not as much opinions as wanted are included.
A 1.8% 30-day mortality was found in literature for PS systems. This percentage seems very high, since UMC Utrecht only uses methods with a mortality rate lower than 0.01%, and they do use a PS system. [Dr. M.C. Kruyt, personal communication, 06/01/2018]

9.2 Study population

In this research, only ordinary OVCFs are taken into account, while often more complications are present when fixation is needed. Most of the time, the facet joints, needed for CC-SLR, are damaged or even removed. [Dr. M.C. Kruyt, personal communication, 06/12/2018] It has to be researched whether this method could still be used if the facet joints are damaged, and if not, whether the wires could be secured elsewhere.

While most OVCFs occur in elderly, [1] the biggest problems with OVCFs appear in children and young adults. For them, the use of PMMA is undesirable because the bone-PMMA interface will always exist which can be provocative for PMMA breaking out. Also, it does not dissolve in the course of time and thus remains a solid structure. This problem is less present in elderly, so in future studies, researchers should also focus on the osteoporotic group containing children and young adults. [Dr. M.C. Kruyt, personal communication, 05/18/2018] While the concept models raised in this study might work properly in elderly, it is unknown whether it would also work properly in children and young adults. The concept models have to be researched before its implementation in general, but especially in children and young adults.
Furthermore, an OVCF will heal in approximately 1 year because of bone growth. Therefore, degradable materials are more desirable since the material will be degraded once the fracture is healed. [Dr. M.C. Kruyt, personal communication, 06/01/2018] Inflammation at the moment of degradation has to be taken into account because it is undesirable to inflict inflammation. [Dr. M.C. Kruyt, personal communication, 06/12/2018] In children and young

adults, degradable materials are more desirable than in elderly since movement possibilities are less important and there is less time to initiate complications in elderly. [Dr. M.C. Kruyt, personal communication, 06/01/2018]

9.3 Further research

Many suggestions for further research have been given within this study, but the most important parts will be mentioned here once more. First and foremost, the safety and effectiveness of the new methods suggested in this study should be researched. This should first be researched in a model or a cadaver before being tested in animals and later in humans. It should also be researched whether CC-SLR could be performed percutaneously. Furthermore, what material to use for the inflatable ball should be researched further before testing this method in animals and later in humans. Subsequently, what new internal stabilization method works best should be studied. More attention should also be given to the development of using stem cells in the treatment of OVCFs since stem cells are ought to be a promising option in this application.

10 Conclusion

CC-SLR, CC-SLR in combination with PSs and an inflatable ball filled with liquid or little cement balls in the vertebral body are the best of the new methods that were suggested in this study. While CC-SLR or CC-SLR in combination with PSs might not offer an improvement over a PS system right now, it might offer one in the future when a solution is found to make the procedure less invasive. An inflatable ball filled with liquid or little cement balls in the vertebral body could offer an improvement in comparison with VBS, since leakage of PMMA is no longer present and removal of the materials no longer forms a problem. Currently, some methods in development, like stem cells, could also offer an improvement when enough research is conducted into the safety and effectiveness of these methods.

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Appendix A – Abbreviations

ALVF	Adjacent level vertebral fractures
APVA-PM	Acetalized polyvinyl alcohol porous material
BKP	Balloon kyphoplasty
BMD	Bone mineral density
CaP	Calcium phosphate
CSH	Calcium sulfate hemihydrate
CC	Crisscross
CC-SLR	Combination of crisscross fixation and spinal loop rectangle
hPSC	Human perivascular stem cell
MMA	Methyl methacrylate
MSC	Mesenchymal stem cell
OVCF	Osteoporotic vertebral compression fracture
PDMS	Poly(dimethyl siloxane)
PET	Poly(ethylene terephthalate)
PMMA	Poly(methyl methacrylate)
PP	Poly(propylene)
PTH	Parathyroid hormone
PS	Pedicle screw
PVC	Poly(vinyl chloride)
RF-TVA	Radiofrequency-targeted vertebral augmentation
SLR	Spinal loop rectangle
SLW	Sublaminar wiring
Sr CaP	Strontium-containing calcium phosphate
Tg	Glass transition temperature
UHV-PMMA	Ultrahigh viscosity poly(methyl methacrylate)
VBS	Vertebral body stenting
VP	Vertebroplasty

Appendix B – Interview

1. Wat is de indicatie voor het overgaan tot een niet-medicamenteuze behandeling?
2. Hoe werkt de methode waarvan u gebruik maakt bij het fixeren van gefractureerde osteoporotische wervels?
3. Waarom wordt er geen gebruik gemaakt van vertebroplastiek of kyphoplastiek?
4. Welke complicaties komt u tegen en wat is de frequentie van deze complicaties?
5. Wat is de oorzaak van deze complicaties?
6. Raken schroeven vaak los en zo ja, vormt dit een klinisch probleem?
7. Vinden er na behandeling vaak nieuwe breuken plaats en wat wordt er aan deze nieuwe breuken gedaan? Zijn deze breuken in dezelfde wervel of een aanliggende?
8. Wat zijn volgens u eisen voor een fixatie- of stabilisatietechniek voor osteoporotische wervels?
9. Hoe lang moet de techniek meegaan?
10. Hoe lang gaat botcement mee?
11. Hoe lang gaat een pedikel schroef systeem mee?