Author's response to reviews

Title: Radiographic and safety details of Vertebral Body Stenting: results from a multicenter chart review

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Author's response to reviews: see over
Dear reviewers,

we are thankful for the constructive criticism and have answered to your comments on a point by point basis, as well as highlighted all changes in the revised manuscript in grey. We apologize for the confusion we caused by mixing up the study designs of two separate undertakings, a preparational pre-study phase which the current article deals with, and an ongoing RCT which cannot be described yet. We think the two different settings are now clarified with our comments and changes in the manuscript. We have added two newly published studies about VBS and by discussing their results we realized that key information for assessing or comparing the realignment is e.g missing in the RCT about BKP vs VBS (Werner et al, new reference) and in many other studies: the preoperative local kyphosis. This parameter determines how much reduction potential a fracture has per se, and this potential does naturally limit the performance of any system aiming at kyphosis reduction. We feel that the detailedness and the important aspects of radiological description of any study dealing with vertebral fractures and their internal reduction should be more stressed in future publications, and we have tried to give an example with our analysis that may set a new standard. Fracture types and age, deformation extent, kyphotic angles, Beck Indices and alternative Beck Indices belong to the key set of covariates that influence realignment with any system and they are hardly completely assessed in any of the respective current and past publications in the literature. We hope that this strength of our article is appreciated by you.

Sincerely, the authors

Reviewer's report - VBS

Title: Early results of Vertebral Body Stenting: a multicenter series of the first 100 cases

Version: 1 Date: 3 March 2013

Reviewer: Eyal Itshayek

Reviewer's report:

Major Compulsory Revisions

1. The authors describe the use of a recently used vertebral stenting system for the augmentation of vertebral compression fractures. They report the results of a prospective multicenter observational case series. However, they do not report if they had an IRB approval for the study or not. If they had one it should be mentioned and if they did not have one then it is up to the journal's policy whether to publish the paper or not.
Our answer: given the comments of reviewer 1 and 2 about the IRB we became aware of the misunderstanding we have created and accordingly rephrased the description of our setting. “in the framework of a prospective international multicenter ....” meant the preparational and pilot phase of case report form development for the meanwhile recruiting and still ongoing international multicenter RCT (VBS vs BKP) which does of course have IRB approval and is registered in clinicaltrials.gov. For developing and testing the CRFs we retrospectively transcribed radiographic data and procedural information of the 100 cases we have included in the current paper. The new data collection setting reads:

Abstract

Methods: during the planning phase of an ongoing international multicenter RCT, radiographic, procedural and followup details were retrospectively transcribed from charts and x-rays for developing and testing the case report forms. Radiographs were centrally assessed at the institution of the first/senior author.

Text body

Background:

 ...

The aim of the current analysis was to describe clinical and radiographic results of the new endovertebral stenting system obtained by chart review of the first 100 cases.

Methods

 ...

Information was retrospectively transcribed from charts and radiographs with clinical and radiographic case report draft forms at the University hospital Bern, Switzerland; the University hospital Muenster, Germany; BG Unfallklinik Frankfurt, Germany; hospital Mutterhaus der Borromäerinnen, Trier, Germany; Aalborg Fysiurgiskeclinic, Denmark; the University hospital of Rostock, Germany, and the cantonal hospital Fribourg, Switzerland. The data were then entered into the MEMdoc online database of the Institute for Evaluative Research in Medicine at the University of Bern [8]. Radiographs were centrally assessed at the institution of the first/senior author. No patient outcomes like VAS, ODI or EQ-5D were recorded.
The study protocol for the ongoing international multicenter RCT was partially applied for data collection of the current analysis:

...

2. The main goal of treating vertebral compression fractures is pain control. However, the authors choose not to collect data regarding pain, disability or any other clinical outcome measure. Choosing to do so, the title of the paper should not be early results but radiographic evaluation or safety of the system. That should be changed in the discussion as well.

Our answer: we welcome this suggestion and have changed the title to –

**Radiographic and safety details of Vertebral Body Stenting: results from a multicenter chart review**

In accordance with the new title and since the paper is very long anyway we have deleted the results and discussion about pain medication consumption.

3. The authors choose to limit their inclusion criteria to fractures between the 10th thoracic vertebra and the 5th lumbar vertebra although kyphoplasty is indicated for the treatment of fractures between the 5th thoracic vertebra and the 5th lumbar vertebra. The reason for choosing so should be discussed. That fact might also explain the relatively big amounts of cement that were injected into the vertebrae. It is well documented that 1cc of cement is enough for a thoracic vertebra and 3cc are enough to achieve pain control in the lumbar region.
Our answer: the inclusion criteria were derived from the producer’s recommendation since at the time of data collection only two stent sizes were available (20mm, 15mm). Meanwhile, a third and smaller size (13 mm) for the thoracic vertebral bodies cranially to Th10 is available. The paragraph “Technical data” does now also present the available stent sizes and recommended levels of application.

Regarding cement volumes we refer to our data from the SWISSpine BKP cohort (Diel et al. Spine J. 2010 Nov;10(11):961-71), where we see that higher cement volumes are applied in the routine clinical setting and that in this setting 4.5ml are the threshold for achieving the mean pain relief of the sample with a higher likelihood (presentation at DWG annual conference 2012, paper submitted to ESJ).

Given that the expanded stent creates an even larger, because more stable cavity after balloon deflation, and that we have only worked with lower thoracic and lumbar vertebrae, we consider the cement volumes to be of a dimension we would consider as expected. Thaler et al (new reference), for example, report an average of 7.3ml cement filling volume in their VBS group of 27 patients.

4. About 76% percent of the patient had fracture - procedure interval of up to six weeks. Osteoporotic vertebral compression fractures are usually self limiting.
disease and most of the fractures usually heals within six weeks. Old patients harboring other co-morbidities are patients we want to keep mobile and ambulating. That is a good reason for early intervention however the patients presented here had average age of around 70 year, relatively young. That point should be discussed as it might explain the extent of correction described in the paper. Usually fresh fracture allows better correction.

Our answer: the reviewer’s comments show that our summary of time intervals was not well chosen. 50% of the fractures were treated within three weeks after fracture occurrence. This is probably the better interval to mention. The text was changed accordingly: “The time between incidence of fracture occurrence (acc. to patient) and treatment was less than one week in 24 (OP 16.3) %, up to three weeks in 66 (OP 58) % and more than three weeks in 34% (OP 42) %.

We agree that the extent of correction is influenced by fracture age, but our analysis did not show a strong correlation between fracture age and extent of fracture reduction, most probably because of the above mentioned majority of “younger” fractures. We do rather believe and see that the extent of preoperative deformity and sclerotic intravertebral zones have an influence on the reduction and have discussed both aspects already.
5. The ASA status was reported in the results but was not discussed later. It should be discussed or deleted.

Our answer: since we did not see any major complications related to ASA status we deleted its description in the results paragraph in order not to further lengthen the discussion.

6. According to table 2 four patients underwent an intervention due to what the author named neurocompression, it more then one percent of complications that was mentioned in the discussion.

Our answer: the reinterventions for what the surgeons had labelled neurocompression happened 27-30-87-170 days after the intervention. The 1% complication rate mentioned in the discussion referred to the intraoperative complications.

7. The details of the VBS system should be mentioned as soon as the VBS abbreviations being presented into the text.

Our answer: we wrote the following paragraph in the Introduction: “Therefore the Vertebral Body Stenting System (VBS) was developed which uses a balloon-catheter-mounted stent that is expanded by inflating a balloon inside the vertebral body. With its intrinsic mechanical stability, the expanded rigid stent construct keeps the created cavity open after balloon deflation until PMMA-based cement is injected and has cured [7]. “ We feel this is sufficiently detailed for an introduction paragraph. The paragraph “Technical data”, however, was now moved up to the Methods section. We consider this as a good compromise and hope it meets the reviewer’s acceptance.

Reviewer’s report:

In my opinion this study needs major revision, because there are strong concerns about this study:

1. This study is presented as a prospective study, for such a study design we do need an ethic vote other than that I can not consider this study for publication

Our answer: we refer to similar comments and our answers to reviewer 1. We have discarded the term “prospectively” as the mode of data collection because it actually referred to the ongoing RCT and not to the current chart review. We apologize for the confusion we have caused.
2. Only radiograph are collected, to give a statement about this new operation system we do need some clinical data like VAS, ODI or SF36.

Our answer: given the setting and new title of the study that reviewer 1 had suggested and our according focus on radiographic and safety parameters of VBS, no outcome data collection and description is implied. However, we added the aspect of a minimum necessary local back pain intensity of VAS >4 (scale 0-10) corresponding with the level of fracture, as part of the inclusion criteria, as it is written in the RCT study protocol. How the individual centers captured and recorded the pain intensity was left to their decision, since only the physician based forms (surgery, followup, radiology) were tested and developed, and for outcome documentation in the RCT validated and standard outcome instruments are used. We are convinced that pain alleviation will be neither better nor worse than that of other vertebral augmentation techniques (see new reference Werner et al), but that there especially is a potential for better realignment, depending on fracture type. This is why we chose to report the radiographic aspects of this pilot group sooner and in more detail.

3. I miss a study protocol please add this to methods

Our answer: a comprehensive study protocol was composed for the RCT and it represented the basis for our approach, which was, however, an observational one and based on image and chart data. We have added this point to the methods section.

4. Follow up time is not defined: We do need well defined follow ups like pre/posoperatively after 6 weeks, 12 week, 6 months or 12 months, an average of of 119 days for the follow-ups (range 3-468 days) is not adequate.

Our answer: the mean FU time and range describes all followups that were theoretically available for the data analysis. The revision and refracture interval of observation was 3-4 months, which corresponds with the time frame where most refractures typically happen. For radiographic analysis we took the last available image information which was largely in the 6 months followup time window.

5. Discussion with 22 References are not enough, I miss current study e.g. high viscosic cement studies, radiofrequency kyphoplasty and critical disput with the high cement exclusion rate.

Our answer: we have added four new references (2 new VBS studies, 1 study about rf kyphoplasty, 1 study about high viscosity cement) and also extended the discussion further. 2 references were
discarded after eliminating the pain medication paragraph. With regards to the “high” cement extrusion rates we do only partially agree, since e.g. the osteoporotic group had a 23.8 % extrusion rate, despite an ideally overfilling of the VB as suggested by Klezl. The aspects of learning curve and normally viscous cement that was used in this series are discussed, as well as the evtl. further reduction of leakage rates with new high viscosity cements or rf kyphoplasty.

Discussion

The current case series presents the short-term results of a very early series of the first 100 cases treated with the VBS system. In the meantime four other studies have presented clinical and radiographic outcomes of the VBS system, but all patient samples were considerable smaller (~ 50-20 cases) [10-13]. Overall, good restoration of vertebral body height and alignment were obvious, but a direct translation of realignment into a significantly reduced rate of adjacent vertebral fractures, as suggested in the biomechanical literature, could not be shown in our series [14], and much larger case numbers will be needed for a conclusive assessment of this aspect.

VBS was developed for overcoming the weakness of the BKP system in incompletely maintaining the restored vertebral body realignment and height that is achieved with a fully inflated balloon [15, 16]. This weakness of BKP leaves a considerable one third of treated cases without an appreciable height restoration [2]. The percentage and the overall extent of realignment shall be improved with VBS based on the principles of balloon kyphoplasty and vascular stenting. Using VBS, the stent remains within the newly created vertebral cavity so the balloon can be removed after deflation while preventing the vertebral body from collapsing, so that, in an ideal scenario, a virtually physiological vertebral body height and shape can be restored and preserved. In their recent RCT, Werner et al did not find significant differences in vertebral kyphosis correction between BKP and VBS. Both systems achieved around 4.6° of mean reduction [13]. Despite a sufficiently powered analysis and presumably
well balanced fracture characteristics, preoperative kyphotic deformity angles of the two groups
were not reported, which, according to our findings, have an influence on the reduction potential of
a fracture. Moreover, stratified results by fracture type were not reported, which may have revealed
differences between the two therapies. Thaler et al could only achieve an average 3.5° reduction of vertebral kyphosis in 27 patients, but the mean preoperative Beck Index of 0.87 implies a smaller reduction potential than that of our group (preop 0.73), which may explain the better reduction of 4.2° in the current study [12].

Using a different unit for describing re-alignment but kyphotic angles, Maestretti et al reported Beck Index improvements of 0.14 in their traumatic BKP case series treated with calciumphosphate cement [17] and Krüger et al of about 0.07 in their series of osteoporotic incomplete burst fractures [18]. However, in the latter series the preoperative BI values were around 0.8, whilst those in the Maestretti series were 0.7 and hence better comparable with the extent of VB deformation in our series. The overall BI improvement we found was 0.2, and even 0.26 in an idealized scenario ignoring the non-moving and poor-moving fractures. These values do also make clear that they can only be achieved in fractures with preoperative BI values of about 0.7 or lower.

The indication for applying a vertebral augmentation method from the meanwhile available spectrum of “simple” vertebroplasty with no intrinsic mechanical method for height restoration but patient positioning, to balloon kyphoplasty and vertebral body stenting should not only be based on fracture type, patient characteristics and extrusion risks but also on the extent of vertebral body deformation. An only mildly deformed fracture has a generally small realignment potential, and fractures with Beck Indices around 0.8 and local kyphotic angles of 8.5° [18] are probably more suitable for BKP or even VP than fractures with Beck Indices <= 0.7 and local kyphotic angles of 17° [17] where VBS can develop its full realignment potential. As shown in figure 5, about a third and up
to half of the fractures had mean BI improvements of 0.3-0.5, but such extent of restoration can only be achieved with a corresponding preoperative deformity. If not given, the realignment potential of therapies such as VBS and other implant based augmentation technologies is limited by a “ceiling effect”, i.e. restoration of BI to values greater 1.0 is largely impossible and the resulting overcorrection clinically not meaningful. In addition, we could show that reports of Beck Indices and local kyphotic angles are influenced by fracture morphology and should hence be described separately. In our case series there were about 20% biconcave fractures and the relation between vertebral body middle height and posterior wall height, herein introduced as alternative Beck Index is the most appropriate way of describing these fractures. The local kyphotic angle or the original Beck index reflecting the relation between anterior and posterior vertebral height are less suited for a description of biconcave fractures. The anterior-posterior wall relations deal with the important local and the resulting segmental kyphotic deformity which is, based on biomechanical considerations, responsible for increased risks of new adjacent and distant vertebral fractures and patients’ postural decompensation in the kyphotic plane. [14]

Klezl pointed out that kyphosis correction with VBS was better in the traumatic group where even reduction of the fractured endplate with the stent could be achieved with possible implications on future performance of injured discs in young patients [10]. Research suggests that a vertebral trauma and especially a fractured endplate can cause disc cell apoptosis and disc degeneration. [19, 20] The anterior spinal column, especially the fragmented superior endplate could be well reconstructed by the stent provided that it was inserted accurately. Our results confirm these observations where the alternative BI was improved from 0.53 to 0.75 in biconcave but also from 0.64 to 0.85 in crush fractures while it only increased from 0.68-0.79 in wedge shaped fractures. Endplate and mid vertebral height restoration are new aspects in minimally invasive fracture treatment whereas improved realignment and decreased cement leakage was the original goal of the balloon kyphoplasty principle.
Looking at all moving wedge shaped fractures, the local kyphotic angle was even improved by 10°, from preoperative 17.7° to 7.6°. Diel et al report average improvements of 4° with VP [21] and Hulmes reports an average of 6.6° improvement for BKP and VP in his systematic review [2]. In contrast, Papanastassiou et al reported 4.8° kyphotic angle change from baseline for BKP and only 1.7° for VP in their systematic review of randomized and non-randomized controlled studies. Such comparisons highlight the potential of VBS. However, a translation into significantly reduced adjacent fracture rates could not be deduced from our data yet. A 9% rate of new fractures is lower than the 10.4% after BKP but higher than the 8.4% after VP as reported by Papanastassiou [3]. Considering our analysis of cases with new fractures after surgery, the sex distribution in these groups should always be reported since female gender seems to represent a risk factor.

The overall 29% cement extrusion rate we observed is comparable with BKP rates if assessed in an independent fashion. The FREE study reported a 27% extrusion rate whereas the systematic analysis of Hulme et al calculated an only 9% rate based on published literature [2, 22]. In many reports, however, authors have assessed their own extrusions which probably lead to a gross underreporting. Thaler et al reported a 25.5% extrusion rate in their VBS series and Werner et al had a 20% minor and 10% major leakage rate. In both studies, a viscometer was used [12, 13]. The final rate of symptomatic extrusions in our series was 1% which is lower than the 2.6% in VP and comparable with the 1.3% in BKP reported by Hulme [2]. Klezl had 2 asymptomatic leakages in 20 treated vertebral bodies and Muto had none [10, 11]. Klezl pointed out the more difficult situation in osteoporotic bone where a slight and careful overfilling of cement should be aimed at for achieving a good interdigitation of cement with bone [10]. Considering the 50% osteoporotic fractures in our series and its 23.8% extrusion rate, the cementation challenge in this group seems to have been well met, this despite most surgeons in our series probably not having passed their VBS learning curve yet.
New cementing techniques like radiofrequency kyphoplasty may help to further reduce leakage rates. Kurth et al reported a respectably low rate of only 15.5% in a multicenter study with 186 treated vertebral bodies [23]. High viscosity cement is another promising option for leakage prevention, which has mostly been applied and assessed in vertebroplasty. Georgy found only 8% of moderate or severe leakage in a chart/xray review of 66 treated levels [24], but this figure is not easy to compare with other reports that have not graded leakage into none, mild, and more severe types.

In the meantime, a higher viscosity cement is also available for VBS (Vertecem “V+”) and future studies will have to show if it can help reduce leakage rates to levels comparable with the above cited percentages.

References:


