Peer Review File

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Reviewer A:

The authors performed an animal study looking at a bio-absorbable high-purity Mg cage to be used in ACDF in 24 goats and compared it against iliac autograft. Several issues exist with the current manuscript-

1. High-purity Mg has slower degradation rates theoretically, but I think the authors need to provide better contextualization on a comparison of high-purity Mg vs. conventional Mg cages in an ACDF setting, as previous efforts using Mg cages failed to achieve fusion.

Response: Thanks for this comment. In the Introduction section, we added the contextualization on a comparison of high-purity Mg vs. conventional Mg cages in an ACDF setting in lines 60-69: However, in the ACDF model of goat cervical vertebrae bearing force, although the development of Mg alloys composition and the addition of surface coating methods to improve the degradation of Mg-based cage, such as an AZ31 cage with poly-ε-caprolactone (PCL) coating, porous Mg-Zinc (Zn) alloy cage with a microarc oxidation (MAO)/silicon- (Si-) containing coating and AZ31 cage with Si -containing coating, the whole degradation rate was nonlinear in the 24-week observation period, the early degradation rate was relatively fast, which resulted in the formation of local magnesium ion concentration in tissues. Thus, the bone healing is still poor after implantation of Mg-based cage, and fusion success has never been reported (1-3) (references 11-13 in our study). In addition, in the third paragraph of the Introduction section, we described the advantages of high-purity magnesium materials over conventional Mg materials in order to solve the problem of faster degradation rate in the early stage of traditional magnesium-based material fusion devices.

In goat ACDF models, we compared the high-purity magnesium interbody cages with autogenous iliac implantation based on fusion effect, but high-purity magnesium interbody cages as the experimental group were not compared with conventional Mg cages as the control group. We agree with this comment and will compare the fusion effect between high-purity magnesium interbody cages and conventional Mg cages in our future studies.

References

1. Daentzer D, Willbold E, Kalla K, et al. Bioabsorbable interbody magnesium-polymer cage: degradation kinetics, biomechanical stiffness, and histological findings from an ovine cervical spine fusion model. Spine (Phila Pa 1976) 2014;39:E1220-7.

2. Xu, Haocheng, Zhang, et al. - Evaluation of a Porous Bioabsorbable Interbody Mg-Zn Alloy Cage in a Goat Cervical Spine Model.

3. Zhang F, Xu H, Wang H, et al. Quantitative analysis of near-implant magnesium accumulation for a Si-containing coated AZ31 cage from a goat cervical spine fusion

model. BMC Musculoskelet Disord 2018;19:105.

2. Was autogenic iliac bone used in previous studies?

Response: Thanks for this comment. The autogenic iliac bone has been used in previous studies. The study design in references 1-3 (references 11-13 in our study) were similar to ours. In these studies, the application of Mg-based interbody cages was investigated in the goat cervical ACDF model, in which the autogenic iliac bone served as a control. In the references 2 and 3 (references 12 and 13 in our study), autologous ilium bone was used to fill the hole in the middle of the interbody cages.

References

1. Daentzer D, Willbold E, Kalla K, et al. Bioabsorbable interbody magnesium-polymer cage: degradation kinetics, biomechanical stiffness, and histological findings from an ovine cervical spine fusion model. Spine (Phila Pa 1976) 2014;39:E1220-7.

2. Xu, Haocheng, Zhang, et al. - Evaluation of a Porous Bioabsorbable Interbody Mg-Zn Alloy Cage in a Goat Cervical Spine Model.

3. Zhang F, Xu H, Wang H, et al. Quantitative analysis of near-implant magnesium accumulation for a Si-containing coated AZ31 cage from a goat cervical spine fusion model. BMC Musculoskelet Disord 2018;19:105.

3. Autograft was used in conjunction with HP Mg cage which might confound the results regarding fusion, as iliac autograft is not generally used clinically with a PEEK cage.

Response: In the ACDF, some investigators still used fill the autologous bone in the middle hole of polyetheretherketone (PEEK) cages, aiming to achieve better bone fusion. Currently, PEEK with (auto) graft is frequently used for interbody fusion as shown in the following references 1-7.

In the following references 8 and 9 (references 12 and 13 in our study), iliac autograft was used in the middle hole of the fusion cages, but the interbody fusion was not observed during the postoperative observation period. In the present study, we investigated the application of magnesium based interbody cage in a goat ACDF model, in which autogenous iliac bone was filled in the middle hole of the cage. After 24 weeks, perforation fusion was observed between the upper and lower vertebral body. These results were different from those obtained with conventional Mg cages because the application of conventional Mg cages failed to achieved cervical vertebral fusion in goats ACDF model. Thus, the use of autograft in conjunction with HP Mg cage may not bias our findings.

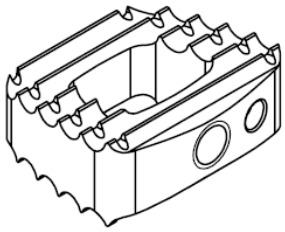
In our future studies, we will improve the Mg-based interbody cages and will apply these cages without autogenous bone, which may demonstrate the true value of absorbable Mg-based interbody cages.

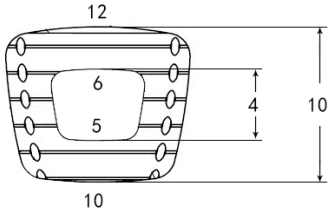
References

1. Arts, M., B. Torensma and J. Wolfs, Porous titanium cervical interbody fusion device in the treatment of degenerative cervical radiculopathy; 1-year results of a prospective controlled trial. Spine J, 2020.

2. Liu, J.M., et al., A comparison of local bone graft with PEEK cage versus iliac bone graft used in anterior cervical discectomy and fusion. Clin Neurol Neurosurg, 2017. 155: p. 30-35.
3. Kim, S.H., et al., Polyetheretherketone Cage with Demineralized Bone Matrix Can Replace Iliac Crest Autografts for Anterior Cervical Discectomy and Fusion in Subaxial Cervical Spine Injuries. J Korean Neurosurg Soc, 2017. 60(2): p. 211-219.
4. Kasliwal, M.K. and J.E. O'Toole, Clinical experience using polyetheretherketone (PEEK) intervertebral structural cage for anterior cervical corpectomy and fusion. J Clin Neurosci, 2014. 21(2): p. 217-20.
5. Oh, S.H., et al., ACDF Using the Solis Cage with Iliac Bone Graft in Single Level: Clinical and Radiological Outcomes in Average 36 months Follow-up. Korean J Spine, 2013. 10(2): p. 72-7.
6. Hellbusch, L.C., W.J. Spangler and A. Bowder, Radiographic PEEK double-lucency finding after anterior cervical discectomy and fusion with local autograft and PEEK spacer: a preliminary study. J Neurosurg Spine, 2012. 16(3): p. 248-50.
7. Park, H.W., et al., The efficacy of the synthetic interbody cage and Grafton for anterior cervical fusion. Spine (Phila Pa 1976), 2009. 34(17): p. E591-5.
8. Xu, Haocheng, Zhang, et al. - Evaluation of a Porous Bioabsorbable Interbody Mg-Zn Alloy Cage in a Goat Cervical Spine Model.
9. Zhang F, Xu H, Wang H, et al. Quantitative analysis of near-implant magnesium accumulation for a Si-containing coated AZ31 cage from a goat cervical spine fusion model. BMC Musculoskelet Disord 2018;19:105.

4. The fact that fusion area was less than 30% was worrisome- what is the percentage of surface area accounted for by the autograft in the HP Mg cage?
Response: The fusion cage is shown in Figure 1 of our study. The three-dimensional structure and the plane of the fusion cage contacting with the upper and lower vertebral bodies are shown in the following figure. It is an irregular plane. Autogenous iliac bone localizes at the interface between the cage and the upper / lower vertebral body plane, and this interface is similar to the two isosceles trapezoids. The big trapezoid is sized 12×10×10 mm; Autogenous iliac bone localizes on the small trapezoid which is sized 6×5×4 mm. The cavity in the middle of cage is filled with autogenous iliac bone, and the surface area of the middle-hole plane accounts for about 20%. This information was added to the revised paper: lines112-114.





5. Also, why was there gas accumulation?
Response: Mg dissolves in aqueous solution according to the following equations.

Anodic reaction: $Mg \rightarrow Mg^{2+}+2e$. Cathodic reaction: $2H_2O +2e \rightarrow H_2+2OH^-$; $Mg^{2+}+2OH^- \rightarrow Mg(OH)^2$. Therefore, with the degradation of magnesium materials, H_2 gas will be produced, and in the previous studies of Mg-based materials intervertebral fusion device, gas accumulation is a common phenomenon (Ref 1-3) (references 11-13 in our study).

In our study, gas accumulation was noted at 3 weeks, and it was observed in only 1 goat at 6 weeks, but gas accumulation was absent at other time points. The reason is that the degradation rate of high-purity magnesium material is relatively fast in the early stage, resulting in the phenomenon of gas accumulation. As time goes by, the degradation rate of the high-purity magnesium material slows down, and the formed gas reduces and can be also absorbed via the local microcirculation. Thus, the gas accumulation cannot be observed at 12 and 24 weeks. In our study, bone connection was observed at 24 weeks when the upper and lower vertebrae passed through the intermediate hole of the interbody fusion vessel, indicating that the early gas accumulation would not adversely affect the bone fusion between upper and lower vertebrae.

References

1. Daentzer D, Willbold E, Kalla K, et al. Bioabsorbable interbody magnesium-polymer cage: degradation kinetics, biomechanical stiffness, and histological findings from an ovine cervical spine fusion model. Spine (Phila Pa 1976) 2014;39:E1220-7.

2. Xu, Haocheng, Zhang, et al. - Evaluation of a Porous Bioabsorbable Interbody Mg-Zn Alloy Cage in a Goat Cervical Spine Model.

3. Zhang F, Xu H, Wang H, et al. Quantitative analysis of near-implant magnesium accumulation for a Si-containing coated AZ31 cage from a goat cervical spine fusion model. BMC Musculoskelet Disord 2018;19:105.

6. Implant subsidence rate was not evaluated.

Response: Although the subsidence rate of postoperative vertebral bodies do not represent the curative effect of postoperative, high cage subsidence rates with high treatment levels remain controversial [1], but in the long-term follow-up after surgery, subsidence rate is an important parameter. In most studies about ACDF, subsidence > 3 mm is used as a threshold [2]. In the present study, postoperative imaging failed to identify the apparent implant subsidence in both groups because the height change of the vertebral body was less than 3 mm. According to the comment, we added the descriptions about implant subsidence lines 181-182 (During the observation period, obvious settlement of implant was not observed in both groups).

References

[1]. Kao, T.H., et al., Risk factors for subsidence in anterior cervical fusion with stand-alone polyetheretherketone (PEEK) cages: a review of 82 cases and 182 levels. Arch Orthop Trauma Surg, 2014. 134(10): p. 1343-51.

[2]. Lee, H.C., et al., Comparison of radiological outcomes and complications between single-level and multilevel anterior cervical discectomy and fusion (ACDF) by using a polyetheretherketone (PEEK) cage-plate fusion system. Medicine

(Baltimore), 2019. 98(5): p. e14277.

In the present study, we did not observe the implant subsidence > 3 mm, and thus the implant subsidence rate was not compared between two groups. However, there was difference between two groups, and ΔDSH was compared.

7. How would the use of plate and screws affect the assessment of mechanical strength of the HP Mg cage?

Response: Developments in ACDF techniques have led to the introduction and routine application of anterior plate fixation in order to provide additional stability [1]. However, patients who underwent ACDF with a cage-plate technique have better radiographic outcomes with significantly less subsidence and better restoration of cervical lordosis compared with patients who underwent ACDF with a cage-only technique [2]. However, this cage-only technique has its own complications, such as cage subsidence, cervical dislocation, and cervical kyphosis [3].

The compression test before fusion implant showed the modulus of elasticity in compression will was 609.43 ± 52.16 MPa, the yield strength was 151.59 ± 8.34 MPa and compressive strength was 392.62 ± 16.23 MPa. The mechanical strength is fully competent to maintain intervertebral height.

As for the high-purity magnesium cage in the present study, no study has revealed the successful bone fusion in the early stage with the magnesium based interbody cage. Thus, in our study, the plate was adopted to ensure the stability of the segments, aiming to achieve the successful bone fusion. Therefore, in our study, the high-purity magnesium cage was compared with autologous ilium bone, and plates and screws were used in the two groups.

Of course, the anterior plate may maintain the intervertebral disc height and strengthen the mechanical support of fusion cage, thus affecting mechanical evaluation of the performance of fusion mechanical support. In our future studies, we will improve the magnesium-based cages, and compared the high-purity magnesium-based cages with traditional cages.

References

[1]. Song, K.J. and K.B. Lee, A preliminary study of the use of cage and plating for single-segment fusion in degenerative cervical spine disease. J Clin Neurosci, 2006. 13(2): p. 181-7.

[2]. Cheung, Z.B., et al., Comparison of Anterior Cervical Discectomy and Fusion With a Stand-Alone Interbody Cage Versus a Conventional Cage-Plate Technique: A Systematic Review and Meta-Analysis. Global Spine J, 2019. 9(4): p. 446-455.

[3]. Kwon, W.K., et al., Analysis of Associating Factors With C2-7 Sagittal Vertical Axis After Two-level Anterior Cervical Fusion: Comparison Between Plate Augmentation and Stand-alone Cages. Spine (Phila Pa 1976), 2017. 42(5): p. 318-325

Reviewer B:

In this paper, a new type of fusion cage based on high purity magnesium is introduced.

Overall, the manuscript is in a good shape. At the same time, there are still some places to be modified.

1. The current title does not reflect the main advantages of the novel fusion cage. Please revise.

Response: Thanks for this comment. We have revised the title into "Bioabsorbable high-purity magnesium interbody cage: degradation behavior, interbody fusion, and biocompatibility from a goat cervical spine model.

2. It is recommended to appropriately introduce the clinical needs of anterior cervical discectomy and fusion, and the reason why the related materials are required to be improved in the introduction section.

Response: According to this comment, we added following descriptions:

The anterior cervical decompression and fusion (ACDF) has been a standard treatment for the cervical degenerative disease. Autologous iliac bone implantation is a gold standard for the intervertebral fusion, but patients still have long-lasting pain, damage to blood supply and infection at the site of implantation (1-3). Currently, the commonly used cervical interbody fusion cage is mainly made of non-absorbable materials such as polyether ether ketone (PEEK) and titanium，which may cause implant subsidence and segment instability, and induce chronic inflammatory response (4-5).

References

1. Lalk, M., et al., Fluoride and calcium-phosphate coated sponges of the magnesium alloy AX30 as bone grafts: a comparative study in rabbits. J Mater Sci Mater Med, 2013. 24(2): p. 417-36.

2. Silber, J.S., et al., Donor site morbidity after anterior iliac crest bone harvest for single-level anterior cervical discectomy and fusion. Spine (Phila Pa 1976), 2003. 28(2): p. 134-9.

3. Banwart, J.C., M.A. Asher and R.S. Hassanein, Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. Spine (Phila Pa 1976), 1995. 20(9): p. 1055-60.

4. Maldonado-Naranjo AL, Healy AT, Kalfas IH. Polyetheretherketone (PEEK) intervertebral cage as a cause of chronic systemic allergy: a case report. Spine J 2015;15:e1-3.

5. Li ZJ, Wang Y, Xu GJ, et al. Is PEEK cage better than titanium cage in anterior cervical discectomy and fusion surgery? A meta-analysis. BMC Musculoskelet Disord 2016;17:379.

3. Lines 40-51，please simplify the discussion of PEEK as a spacer and replenish the content of advantages and disadvantages of autologous bone grafting.

Response: According to this comment, we simplified the discussion of PEEK as a spacer, and added advantages and disadvantages of autologous bone grafting. In the Introduction section, we added following descriptions: The anterior cervical decompression and fusion (ACDF) has been a standard treatment for the cervical degenerative disease. Autologous iliac bone implantation is a gold standard for the

intervertebral fusion, but patients still have long-lasting pain, damage to blood supply and infection at the site of implantation (1-3).

References

1. Lalk, M., et al., Fluoride and calcium-phosphate coated sponges of the magnesium alloy AX30 as bone grafts: a comparative study in rabbits. J Mater Sci Mater Med, 2013. 24(2): p. 417-36.
2. Silber, J.S., et al., Donor site morbidity after anterior iliac crest bone harvest for single-level anterior cervical discectomy and fusion. Spine (Phila Pa 1976), 2003. 28(2): p. 134-9.
3. Banwart, J.C., M.A. Asher and R.S. Hassanein, Iliac crest bone graft harvest donor site morbidity. A statistical evaluation. Spine (Phila Pa 1976), 1995. 20(9): p. 1055-60.

4. All reference numbers should be marked at the final of sentence.

Response: According to this comment, all the reference numbers were placed at the end of sentences.

5. Lines 170-172, please add the experimental data for the total fusion area of the autograft group at twenty-four weeks.

Response: According to this comment, the related information was added to the revised paper: The total fusion area of the autograft group at 24 weeks was 71.17±34.92%.

6. The verb tense in question should be carefully examined.

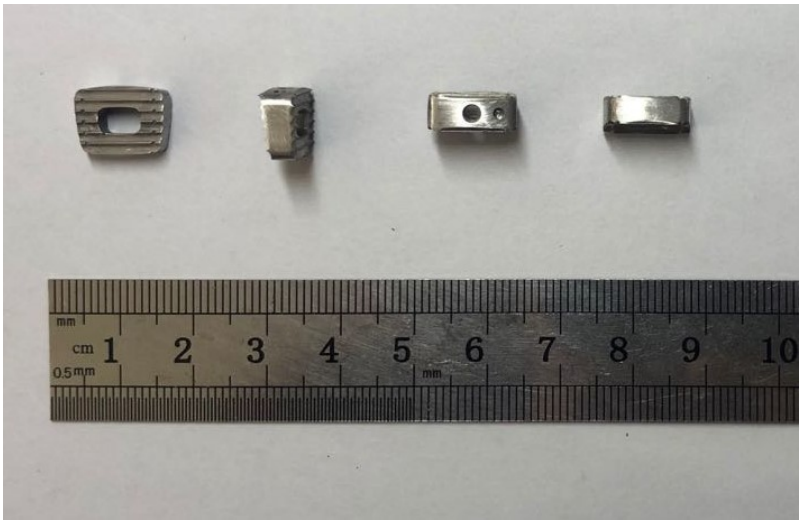
Response: Thanks for this comment. We have revised the paper thoroughly.

7. Lines 294, it is recommended to discuss the shortcomings of magnesium base fusion device compared with autologous iliac bone graft in intervertebral disc fusion surgery.

Response: Thanks for this comment. We have added following descriptions: Of note, the fusion area is still smaller than 30%, and the fusion results in the cage group are markedly worse than in the autogenous ilium group at 24 weeks.

8. It is recommended to replace a hand-drawn scale bar in Figure 1.

Response: Thanks for this comment. We have replaced the figure 1 with following figure.



9. In the references and tables, the font should be uniform.

Response: Thanks for this comment. We have revised this paper thoroughly.