doi: 10.13241/j.cnki.pmb.2019.10.010

大量可降解锌合金板钉体内埋植的早期生物安全性研究 *

邵小夕[1] 王 祥[1] 许方方[1] 戴太强[1] 刘 斌[2] 周功耀[3] 屈功奇[3] 宋 坤[3] 刘彦普[1△]

(1 军事口腔医学国家重点实验室,国家口腔疾病临床医学研究中心,陕西省口腔疾病临床医学研究中心,
空军军医大学口腔医院颌面外科 陕西 西安 710032;
2 军事口腔医学国家重点实验室,空军军医大学口腔医院动物中心 陕西 西安 710032;
3 湖南华耀百奥医疗科技有限公司 湖南 长沙 410600)

摘要 目的:可降解锌合金材料有适中的降解速率,良好的机械性能。目前对于锌合金的体内生物安全性研究多集中于生物体内植入适量的锌合金材料。对于体内植入大量的可降解锌合金材料是否有不良影响,还未见文献报道。本实验从局部和全身反应来研究埋植过量可降解锌合金的早期生物安全性。**方法:**选取 18 只新西兰大白兔分为三组,于皮下植入锌合金内固定板及钉各 4、6、8 块,于术后 3 月、6 月行大体观察,血常规、血生化、血液微量元素检查,内脏和材料周围组织的组织学检查和 ICP-OES 定量检测内脏锌含量观察锌的脏器蓄积情况,材料称重计算每日释放锌含量。**结果:**可吸收锌合金材料表面附着的白色粉末状物质随时间增加而增多,去掉表面白色物质后,材料表面愈加粗糙,术后 3 月、6 月的白细胞计数(WBC),红细胞计数(RBC),谷丙转氨酶(ALT),谷草转氨酶(AST),总蛋白(TP),白蛋白(ALB),尿素氮(BUN),肌酐(Cr),血锌,血镁,血钙、血铜与术前相比无统计学差异。术后 6 月实验动物材料周围组织,心脏、肝脏、脾脏、肺脏、肾脏、性腺未检出异常。术后 3 月、6 月肝脏、肾脏、脾脏的锌离子含量与术前相比无统计学差异。综合计算得到术后 3 月可降解锌合金内固定板的降解率为 9.77± 1.64%,术后 6 月为 11.82± 1.91%,螺钉的降解率术后 3 月为 0.79± 0.66%,术后 6 月为 2.09± 1.00%。**结论:**大量可降解锌合金植入体内的早期生物相容性良好。

关键词:锌合金;降解;生物安全性

中图分类号:R-33; R318.08 **文献标识码:**A **文章编号:**1673-6273(2019)10-1852-06

Early Biocompatibility Study of a Large Number of Degradable Zinc Alloy Plates and Screws Implanted *in vivo**

SHAO Xiao-xi[1], WANG Xiang[1], XU Fang-fang[1], DAI Tai-qiang[1], LIU Bin[2], ZHOU Gong-yao[3], QU Gong-qi[3], SONG Kun[3], LIU Yan-pu[1△]

(1 State Key Laboratory of Military Stomatology, National Clinical Research Center for Oral Diseases, Shaanxi Key Laboratory of Oral Diseases, Department of Cranio-Facial Trauma and Orthognathic Surgery, School of Stomatology, The Fourth Military Medical University, Xi'an, Shaanxi, 710032, China; 2 State Key Laboratory of Military Stomatology, Laboratory Animal Center, School of Stomatology, The Fourth Military Medical University, Xi'an, Shaanxi, 710032, China; 3 Huayao Baiao Medical Technology Co., Ltd, Changsha, Hunan, 410600, China)

ABSTRACT Objective: Degradable zinc alloy materials have moderate degradation rate and good mechanical properties. At present, the research on the biosafety of zinc alloys mostly focuses on implanting an appropriate amount of zinc alloy materials *in vivo*. Whether it has adverse effects on the implantation of a large amount of degradable zinc material in the body has not been reported. This experiment investigated the early biosafety of large number of degradable zinc alloy plates and screws implanted *in vivo*. **Methods:** Eighteen New Zealand white rabbits were divided into three groups. The zinc alloy plates and screws were implanted subcutaneously in groups of 4, 6, and 8. They were observed at 3 months and 6 months after surgery. Blood routine, blood biochemistry, and blood micronutrient examination, histological examination, and quantitative detection of visceral zinc content, and the plates and screws were weighed to calculate the daily release of zinc. **Results:** The white powdery substance adhering to the surface of the zinc alloy increased with time. After removing the white substance, the surface of the material became rougher with time. There was no statistical difference pre-operation and post-operation in the white blood cell count (WBC), red blood cell count (RBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein (TP), albumin (ALB), urea nitrogen (BUN), creatinine (Cr), blood zinc, blood magnesium, blood calcium, and blood copper. No abnormalities were detected in the heart, liver, spleen, lung, kidney, testical, ovary and prostate. There was no significant difference in zinc content in liver and kidney pre-operation and post-operation. The degradation rates of the plates in 3 months and 6 months post-operation were 9.77± 1.64% and 11.82± 1.91%, respectively, and the screws degradation rates

* 基金项目:军事口腔医学国家重点实验室自主研究课题(2017ZA02)

作者简介:邵小夕(1993-),硕士研究生,主要研究方向:生物可降解材料,E-mail: sxxi77@163.com

△ 通讯作者:刘彦普,E-mail: liuyanpu@fmmu.edu.cn

(收稿日期:2018-10-24 接受日期:2018-11-19)

were 0.79± 0.66% and 2.09± 1.00%, respectively. **Conclusion:** The early biocompatibility of a large amount of degradable zinc alloys implanted *in vivo* is good.

Key words: Zinc alloy; Biodegrade; Biocompatibility

Chinese Library Classification(CLC): R-33; R318.08 Document code: A

Artcle ID: 1673-6273(2019)10-1852-06

前言

骨折常需要内固定以保证骨折的复位和稳定。传统的不可降解内固定物,如不锈钢内固定物和钛合金内固定物,常常伴有感染、内植物松动、应力遮挡、过敏等不良反应,常常需要二次手术取出内固定器械[1]。生物可降解材料是目前生物材料领域研究的热门。聚乳酸、可降解镁合金、可降解铁合金材料是目前研究较多的可降解材料,但是他们都有各自的缺点:PLLA 为酸性水解,可能发生无菌性炎症和异物反应[2];镁合金降解速率过快,降解产生大量氢气和产生碱性的局部环境[3];铁合金降解速率过慢,降解产生的产物难以代谢[4]。

可降解锌合金材料是近年来新的研究热门材料。其有适中的降解速率,良好的机械性能[5-8]。目前对于锌合金的体内生物安全性研究多集中于生物体内植入适量的锌合金材料。本课题组前期实验探讨了一种锌合金用于犬下颌骨骨折的内固定器械,结果显示其骨折固定的有效性、良好的降解性和生物安全性[9]。对于体内植入大量的可降解锌材料是否会对全身和局部造成不良影响,还未见文献报道。故本实验将研究植入过量可降解锌合金的生物安全性。

1 材料方法

1.1 实验材料

四孔直连可吸收锌合金接骨板及螺钉(湖南华耀百奥医疗科技有限公司设计并提供)。 型号规格均为:四孔直连接骨板板厚 1.0 mm,板宽 2.6 mm,接骨螺钉直径 2.0 mm,长度 7 mm。产品由环氧乙烷灭菌消毒,无菌袋封装备用(图 1)。

1.2 实验动物

健康新西兰兔 18 只,雌雄各半,重量 2.5-3.0 kg。所有实验动物均由空军军医大学口腔医院动物实验中心提供。动物实验方案由空军军医大学口腔医院动物伦理委员会批准,实验在空军军医大学口腔医院实验动物中心进行(许可证号 SYXK(军) 2015-0001)。将 18 只新西兰兔随机分为三组,分别埋植 4,6,8 块锌合金内固定板及螺钉,每组包含三只实验兔,并保证每组均含有雌、雄兔。术后 3、6 月过量注射麻药处死实验兔并取材分析。

1.3 可吸收锌合金皮下埋植

实验兔术前喂养观察 7 天,兔子无异常表现后,进行兔背部皮下埋植实验。术前常规称重,实验兔由 0.08 mL/kg 速眠新,0.8 mL/kg 的 3%戊巴比妥钠进行肌肉注射麻醉。在兔子背部术区剃去被毛,取俯卧位将兔子固定在手术台上。常规进行消毒铺巾。局部使用利多卡因进行局部浸润麻醉。在兔背部胸腰段的脊柱两侧使用手术刀做切口,钝性分离皮下组织,形成皮下腔隙。将锌合金接骨板两端缝合固定于皮下肌肉表面,并将一枚对应的锌合金螺钉固定于锌合金接骨板旁。生理盐水冲洗术区后缝合关闭伤口。术后连续 3 天,每天一次,于实验兔肌肉注射 80000 U 青霉素, 并按照实验动物的护理标准进行护理,严密观察实验兔的伤口愈合情况。

1.4 大体观察

术中观察埋植情况。术后观察动物常规进食、饮水、活动、伤口愈合、局部反应情况。取材时间点到后,将实验兔进行过量麻药注射死亡,解剖出埋植材料,肉眼观察埋植材料周围组织反应情况和埋植材料的变化并进行拍照记录。

1.5 血液检查

对实验兔术前,术后 3 月,术后 6 月进行抽血并分析:白细胞计数(White Blood Cell, WBC),红细胞计数(Red Blood Cell, RBC),谷丙转氨酶(Alanine aminotransferase, ALT),谷草转氨酶(Aspartate aminotransferase, AST),总蛋白(Total Protein, TP),白蛋白(Albumin, ALB),尿素氮(Blood Urea Nitrogen, BUN),肌酐(Creatinine, Cr)。血液微量元素:锌,镁,钙,铜。

1.6 组织学检查

对实验兔进行安乐死后,取材料周围软组织,心,肝,脾,肺,肾,性腺,前列腺进行 HE 染色,观察组织形态。

1.7 内脏锌检测

取空白及术后 3、6 月取实验兔肝脏及肾脏使用电感耦合等离子体发射光谱(Inductively coupled plasma atomic emission spectrometry, ICP-OES)进行内脏锌含量检测。

1.8 材料称重

称重前,为去除材料表面的降解产物,将材料放入配制的铬酸溶液(200 g CrO_3; 10 g $AgNO_3$; 1000 mL 超纯水)中超声震荡 5 分钟,之后将材料放入无水乙醇超声震荡 5 分钟,然后将材料自然晾干,最后使用分析天平称重记录。

1.9 统计学分析

采用 SPSS22.0 统计软件进行统计学分析, 实验结果以 $\bar{x}\pm$ SD 表示,多组间计量资料的比较采用单因素方差分析,以 $P<0.05$ 表示差异有显著性意义,$P<0.01$ 表示差异有非常显著性意义。

2 结果

2.1 大体观察

术后实验动物恢复良好, 术后 2 天出现二例伤口裂开,经重新清创缝合,抗感染治疗 3 日后,愈合良好。其他创口均为一期愈合,创口无红肿、感染、过敏、产气、露板等情况出现。取材可见锌合金材料被一层纤维囊壁包裹,剖开囊壁,可见锌合金材料在体内出现降解,材料表面粗糙,并布有一层白色粉末状物质(图 1)。

2.2 血液检查

锌合金材料 4、6、8 组术后 3、6 月白细胞计数 (WBC),红细胞计数(RBC),谷丙转氨酶(ALT),谷草转氨酶(AST),总蛋

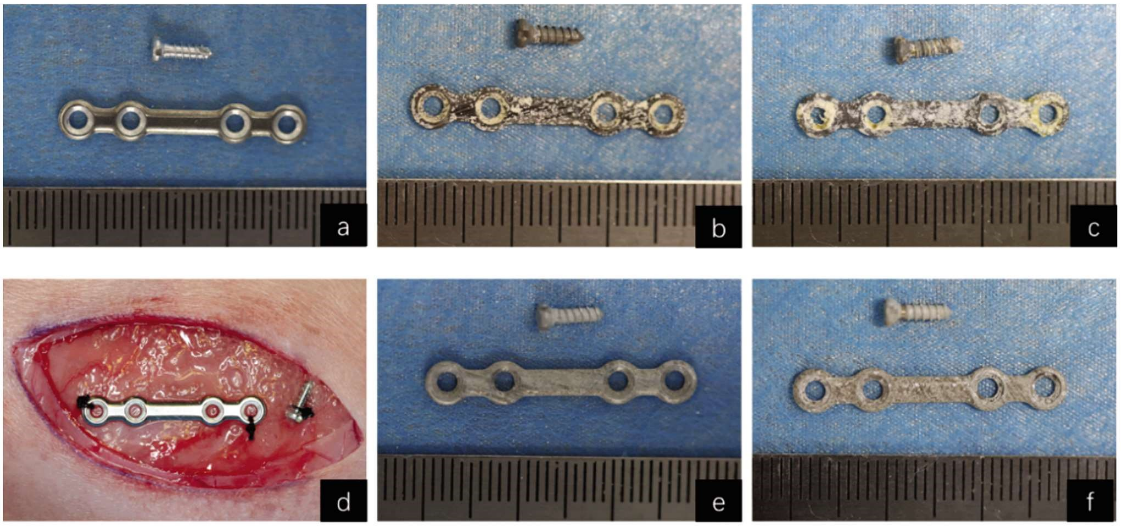

图 1 锌合金板钉术前、术中、术后 3 m、6 m 大体观。a. 锌合金板钉术前大体观，材料表面光滑，有明显金属光泽。d. 锌合金材料植入实验兔背部皮下手术即刻。b. 锌合金板钉术后 3 m 大体观，材料表面有白色粉末状物质覆盖。c. 锌合金板钉术后 6 m 大体观，材料表面白色粉末状物质多于 3 m 组。e. 锌合金板钉术后 3 m 去除表面降解产物后大体观，材料表面略粗糙。f. 锌合金板钉术后 6m 去除表面降解产物后大体观，材料表面比术后 3 m 时更显粗糙。

Fig.1 Zinc alloy plates and screws before surgery and 3 months and 6 months after surgery. a. The zinc alloy surface is smooth and has obvious metallic luster before surgery. d. Zinc alloy material implantation in the rabbit's back subcutaneous immediately after implantation. b. The zinc alloy plate and screw 3 m after the operation, and the surface of the material is covered with white powdery substance. c. After 6 m of implantation, the white powdery substance on the surface of the material is growing more. e. Zinc materials after 3 months' implantation after removal of degradation products, the material surface is slightly rough. f. After 6 months' implantation, after removal of degradation products, the material surface is much rougher than 3 m.

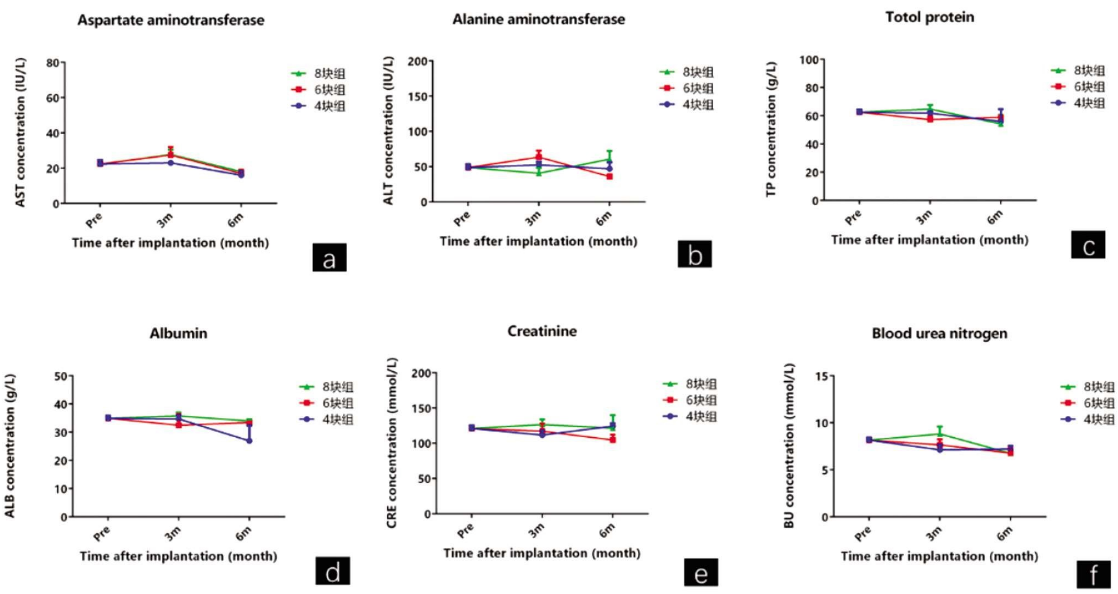

图 2 埋植 4、6、8 块板钉组术前、术后 3、6 月血液 a. 谷草转氨酶 b. 谷丙转氨酶 c. 总蛋白 d. 白蛋白 e. 肌酐 f. 尿素氮 显示术前、术后及各组间差异不具有统计学差异。

Fig.2 Blood biochemistry of three groups before surgery, 3 and 6 months after surgery. a. Aspartate aminotransferase b. Alanine aminotransferase c. Total protein d. Albumin e. Creatinine f. Urea Nitrogen. It shows no differences in preoperative and postoperative results.

白(TP)，白蛋白(ALB)，尿素氮(BUN)，肌酐(Cr)与术前相比无统计学意义，各组间对比无统计学差异 (图 2, 图 3)。血液微量元素：锌，镁，钙，铜术后 3、6 月与术前比无统计学差异，各组间对比无统计学差异(图 3)。

2.3 组织学检查

6 月取材实验动物，对其心脏、肝脏、脾脏、肺脏、肾脏、性腺 HE 染色后进行显微镜观察材料的全身毒性反应。各组内脏未见细胞形态改变，未见炎症细胞浸润，肝脏、肾脏未见有害物质沉积(图 4)。

2.4 内脏锌含量检测

随着材料降解，术后 3、6 月锌在肝脏及肾脏的积累与术前比没有统计学意义，各组间没有统计学差异(图 5)。

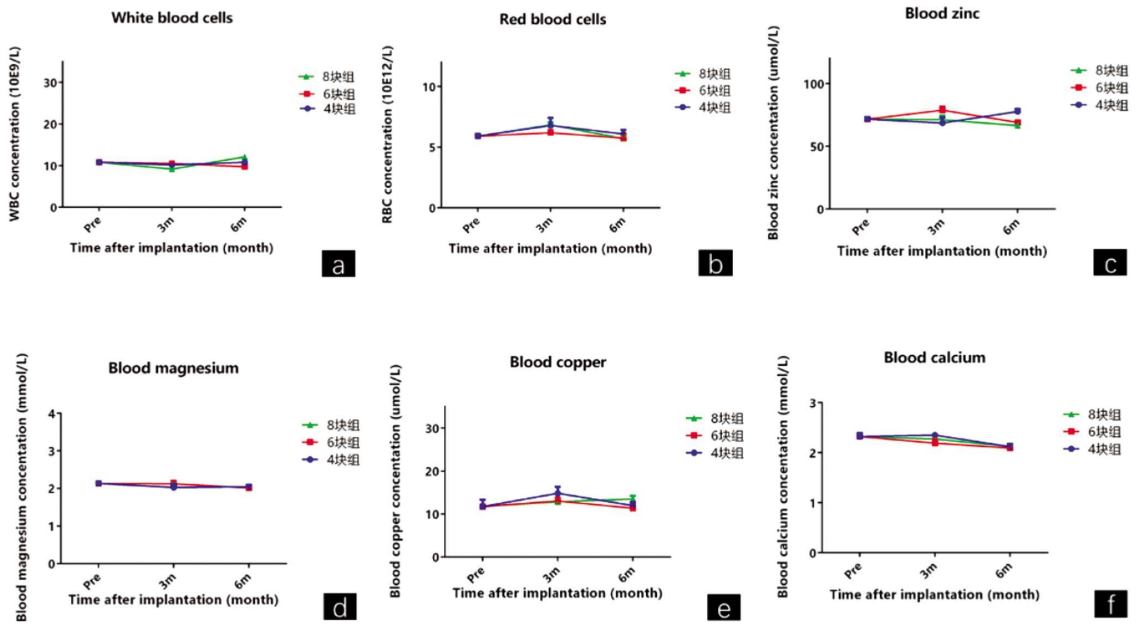

图 3 埋植 4、6、8 块板钉组术前、术后 3、6 月血液 a. 白细胞计数 b. 红细胞计数 c. 血锌 d. 血镁 e. 血铜 f. 血钙 显示术前、术后及各组间差异不具有统计学差异。

Fig.3 Blood normal tests and blood micronutrients of three groups before surgery, 3 and 6 months after surgery. a. White blood cell count b. Red blood cell count c. Blood zinc d. Blood magnesium e. Blood copper f. Blood calcium. It showed no differences in preoperative and postoperative results.

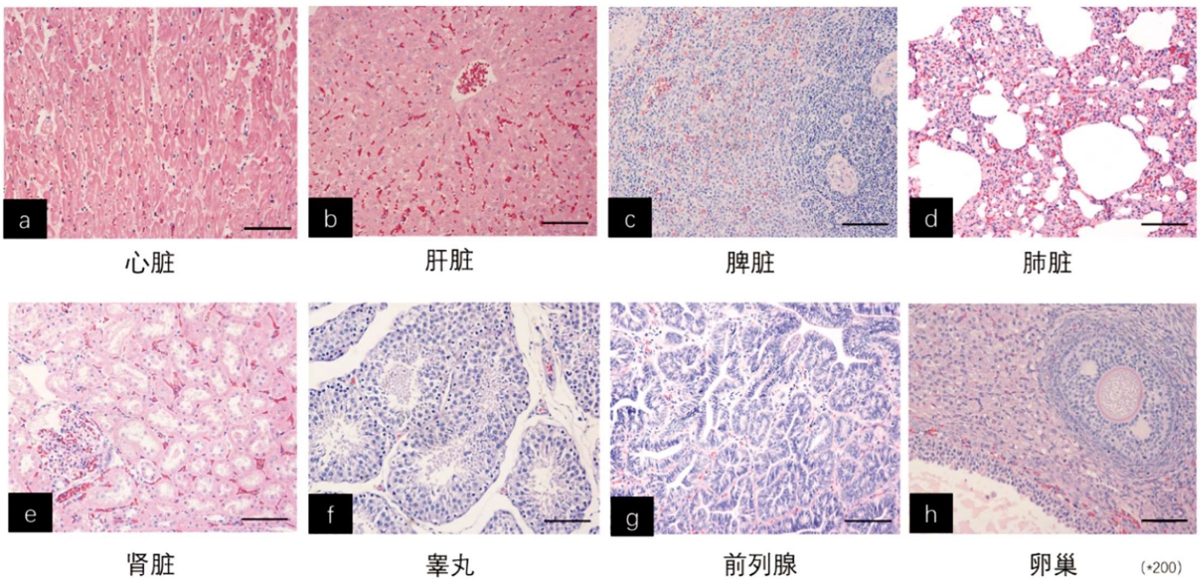

图 4 术后 6 月植入 8 块板钉组 a.心 b.肝 c.脾 d.肺 e.肾 f.睾丸 g.前列腺 h.卵巢（*200）各组内脏未见细胞形态改变，未见炎症细胞浸润，肝脏、肾脏未见有害物质沉积。

Fig.4 8 plates and screws implanted 6 months after surgery. HE staining for a. Heart b. Liver c. Spleen d. Lung e. Kidney f. Testical g. Prostate h. Ovary (scale bar=200) No morphological changes were observed in the viscera of each group. There was no infiltration of inflammatory cells, and no harmful substances deposited in the organs.

2.5 材料称重

术后 3、6 月取埋植材料，去掉表面降解产物后对材料进行称重。术前内固定板重量为 0.553± 0.00625 g，螺钉重量为 0.125± 0.00474 g，3 个月取材去掉降解产物后内固定板重量为 0.501± 0.0144 g，螺钉重量为 0.123± 0.000845 g，6 个月取材去掉降解产物内固定板重量为 0.488± 0.0151 g，螺钉重量为 0.121± 0.00102 g。经统计分析表明，术后 3、6 月的 4、6、8 块组内固定板、钉的重量各组间差异无统计学意义（$P>0.05$）。综合计算得到术后 3 月可降解锌合金内固定板的降解率为 9.77± 1.64%，术后 6 月为 11.82± 1.91%，螺钉的降解率术后 3 月为 0.79± 0.66%，术后 6 月为 2.09± 1.00%。

3 讨论

生物可降解金属材料是目前可降解生物材料领域的热门。

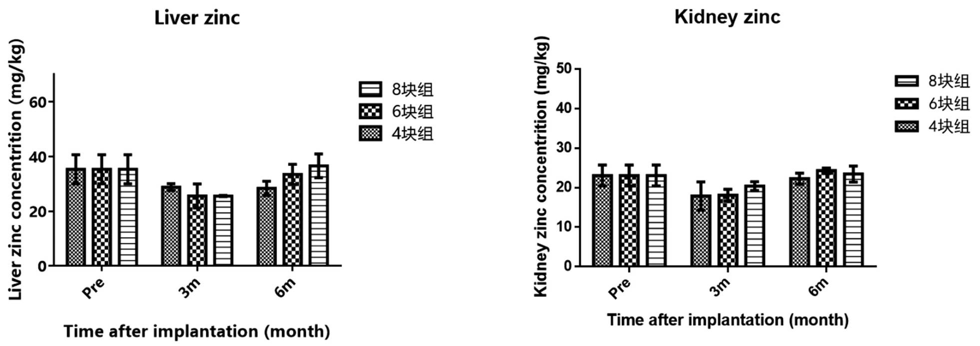

图 5 术后 3、6 月 a. 肝脏锌离子 b. 肾脏锌离子含量变化。显示术前、术后的各组间差异不具有统计学差异

Fig.5 3 m and 6 m postoperative a. liver zinc b. kidney zinc content changes. It showed no differences in preoperative and postoperative

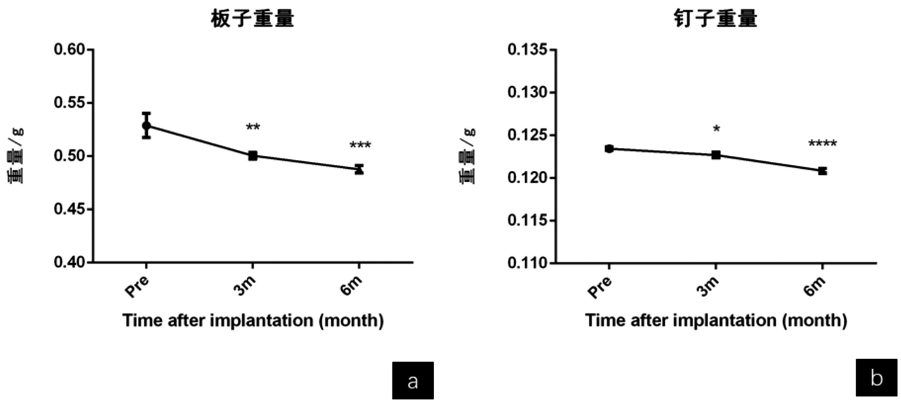

图 6 术后 3、6 月兔皮下板子、钉子重量变化，*$P<0.05$；**$P<0.01$；***$P<0.001$；****$P<0.0001$

Fig.6 3 m, 6 m weight changes of plates and screws. *$P<0.05$; **P<0.01; ***$P<0.001$; ****$P<0.0001$

镁合金作为较早研究的金属可降解材料，其良好的生物相容性和机械性能是其优点[10]。但是，由于镁的腐蚀电位为 -2.37 V，其在体内降解的速率过快，常常不能保证足够机械性能至骨折愈合，且其在降解过程中释放大量氢气导致气肿，生成的降解产物为碱性，导致骨折愈合的微环境不佳，阻碍骨折的有效愈合，阻碍了其大范围的临床应用[11-13]。铁合金也是一种具有良好生物安全性和机械性能的生物材料。但是铁的标准腐蚀电位为 -0.44 V，所以其在体内的降解速率过慢，且降解过程中产生的降解产物较大且较难被人体排出等缺点限制了其作为可降解其作为可降解金属的应用[4,14]。

可降解锌合金因为其良好的机械性能、适宜的降解性能和良好的生物相容性而成为目前可降解生物材料领域的研究热门[15,16]。锌的标准腐蚀电位是 -0.76 V，故锌合金的降解速率要低于镁合金，一定程度上保证了锌合金能够在骨折愈合的早期阶段具有足够的机械性能以促进骨折的愈合[16,17]。与镁的降解过程不同，锌在体内的降解产生 $Zn(OH)_2$ 和 ZnO，不产生氢气，锌离子与体内各重碳酸盐，磷酸盐，氯离子等各种不同离子以及不同浓度的变化产生各种不同的降解产物。且较慢的降解速率也维护了锌合金所在的体内微环境[18]。锌也有良好的抑菌性能。有研究表明锌能有效抑制金黄色葡萄球菌、大肠杆菌和绿脓假单胞菌 [19,20]。且锌有良好的成骨作用 [21-23]，体外培养的 rBMSCs 在锌涂层表面具有更高的碱性磷酸酶活性，且 *OCN*、*Col-I*、*ALP*、*Runx2* 基因表达上调。体内研究显示同样显示良好的新骨形成。锌合金化后能够有效提高纯锌的机械性能以满足骨折愈合所需的内固定强度[24]。

锌是人体必需的微量元素之一，广泛分布于人体的各个组织器官，组成体内多种酶，广泛参与调解体内的代谢[25]。锌的日常人体实际摄入量为 107-231 μmol/d，摄入过量的锌经由肾脏代谢排出，当机体摄入锌量为正常摄入量的 40-50 倍时即可发生急性中毒，当锌的摄入量超过正常量的 10-20 倍时可对机体产生不利的影响[26]。体内各种元素之间会有拮抗作用。肝脏在锌的作用下可合成含有半胱氨酸以及巯基的蛋白质，这些蛋白质与铜的结合力更高，从而时游离铜浓度下降，降低了含铜的酶活性，从而导致脂质代谢异常，高胆固醇血症，心血管异常，心肌细胞氧化代谢紊乱，冠心病，生长发育落后，单纯性骨质疏松等。锌和铁在吸收、排泄方面相互拮抗，在发挥生理功能方面互相影响。过量锌竞争性抑制铁与铁蛋白的结合与释放，影响铁蛋白的储存铁能力，降低体内铁含量，导致低色素小细胞性贫血等。锌、铜在心脏和胰腺中的含量是成负相关关系[27]。锌是保证免疫功能正常发挥的重要元素，但是当机体摄入大剂量的锌时，可抑制免疫细胞的活性和吞噬作用，进而抑制机体的免疫功能。让健康人摄入高剂量锌，结果显示当给锌 4~6 周时，血清锌明显增高，中性多形核细胞对细菌的吞噬作用明显减弱，淋巴细胞对植物血凝素反应降低[28]。

可降解合金是一类特殊的生物材料。良好的生物安全性是其应用所必须的条件。合金在体内植入后开始进行降解，其降解是材料与血液、淋巴液以及各种细胞和组织发生反应的过程，随着可降解合金材料的体内降解，可降解合金材料的各种金属离子析出，与周围体液中各离子结合形成不同的降解产物。且大量产物进入血液、淋巴液进而于全身循环。肝脏、肾脏

对降解产物进行进一步代谢。目前关于可降解金属的研究多在于研究体内植入适量的材料,但是临床上经常会出现大面积骨折的病例,如果可降解合金植入量过多,会不会因为材料同时降解造成大量的金属元素释放进入体内，超过肝肾的代谢能力,进而造成机体伤害,还未可知[15,29,30]。

本课题主要研究机体内植入大量可降解锌合金材料体内的反应。成年实验兔体重大约在 2 kg-8 kg,而成年人体重量大约在 45 kg-90 kg,约为兔子的 5-45 倍,我们设置的实验兔体内植入内固定板钉的组别为 4 块组、6 块组和 8 块组，对应相应兔子人体体重比,相当于人体内植入 20-360 块板钉,此埋植的锌合金板钉范围的最大量已远远超出实际临床上人体内可能埋植的内固定板钉数量。本实验中,3,6 月锌合金板钉材料称重:术后 3 个月锌合金内固定板的降解速率为 0.58 mg/d,螺钉的降解速率为 0.02 mg/d；术后 6 个月锌合金内固定板的降解速率为 0.14 mg/d,螺钉的降解速率为 0.02 mg/d。相当于实验兔埋植量最大组(8 块板钉组)术后 3 个月每天释放锌 4.80 mg,术后 6 个月每天释放锌 1.28 mg。文献报道锌的毒性表现一般出现在摄入量为 100~300 mg/d，急性中毒剂量为 225~450 mg/d,本实验所检测到的锌释放量远低于文献报道产生毒性的剂量[15,29,30]。本实验中,对埋植 4,6,8 块板钉组的实验兔进行大体观察,血液检查,内脏锌离子检测,内脏 HE 切片染色检查,均未检出异常。术后 3 月可降解锌合金内固定板的降解率为 9.77± 1.64%,术后 6 月为 11.82± 1.91%,螺钉的降解率术后 3 月为0.79± 0.66%,术后 6 月为 2.09± 1.00%。为了保证植入材料在体内降解的早期阶段具有较慢的降解速率以保证足够的机械性能,材料表面进行了硬化处理。在表面硬化处理后的材料降解完成后,材料的基底部分会加速降解。本实验的观察时间节点有限,对于材料的降解行为我们还未探索完全,材料在降解后期的降解速率的变化,降解产物会不会长时间在机体内累积,并对机体造成危害,材料在降解完全后机体是否会代谢完全,我们会继续进行观察分析。

参 考 文 献(References)

[1] Unno V F, Ladermann A, Hoffmeyer P. Is hardware removal a necessity?[J]. Rev Med Suisse, 2009, 5(201): 977-980

[2] Bergsma E J, Rozema F R, Bos R R, et al. Foreign body reactions to resorbable poly (L-lactide) bone plates and screws used for the fixation of unstable zygomatic fractures [J]. J Oral Maxillofac Surg, 1993, 51(6): 666-670

[3] Witte F, Kaese V, Haferkamp H, et al. In vivo corrosion of four magnesium alloys and the associated bone response [J]. Biomaterials, 2005, 26(17): 3557-3563

[4] Sotoudehbagha P, Sheibani S, Khakbiz M, et al. Novel antibacterial biodegradable Fe-Mn-Ag alloys produced by mechanical alloying[J]. Mater Sci Eng C Mater Biol Appl, 2018, 88: 88-94

[5] Mostaed E, Sikora-Jasinska M, Drelich J W, et al. Zinc-based alloys for degradable vascular stent applications [J]. Acta Biomaterialia, 2018, 71: 1-23

[6] Zhao S, Seitz J M, Eifler R, et al. Zn-Li alloy after extrusion and drawing: Structural, mechanical characterization, and biodegradation in abdominal aorta of rat[J]. Mater Sci Eng C Mater Biol Appl, 2017, 76: 301-312

[7] Niu J, Tang Z, Huang H, et al. Research on a Zn-Cu alloy as a biodegradable material for potential vascular stents application [J]. Mater Sci Eng C Mater Biol Appl, 2016, 69: 407-413

[8] Tang Z, Niu J, Huang H, et al. Potential biodegradable Zn-Cu binary alloys developed for cardiovascular implant applications [J]. J Mech Behav Biomed Mater, 2017, 72: 182-191

[9] 王祥,屈功奇,戴太强,等.新型可降解锌合金内固定系统用于犬下颌骨骨折固定的研究[J].现代生物医学进展, 2018(07): 1234-1238

[10] Zhao D, Wang T, Nahan K, et al. In vivo characterization of magnesium alloy biodegradation using electrochemical H2 monitoring, ICP-MS, and XPS[J]. Acta Biomater, 2017, 50: 556-565

[11] Witte F, Hort N, Vogt C, et al. Degradable biomaterials based on magnesium corrosion[J]. Current Opinion in Solid State and Materials Science, 2008, 12(5-6): 63-72

[12] Han P, Cheng P, Zhang S, et al. In vitro and in vivo studies on the degradation of high-purity Mg (99.99wt.%) screw with femoral intracondylar fractured rabbit model[J]. Biomaterials, 2015, 64: 57-69

[13] Witte F, Kaese V, Haferkamp H, et al. In vivo corrosion of four magnesium alloys and the associated bone response [J]. Biomaterials, 2005, 26(17): 3557-3563

[14] Mostaed E, Sikora-Jasinska M, Drelich J W, et al. Zinc-based alloys for degradable vascular stent applications [J]. Acta Biomater, 2018, 71: 1-23

[15] Drelich A J, Zhao S, Guillory R J, et al. Long-term surveillance of zinc implant in murine artery: Surprisingly steady biocorrosion rate [J]. Acta Biomaterialia, 2017, 58: 539-549

[16] Gong H, Wang K, Strich R, et al. In vitro biodegradation behavior, mechanical properties, and cytotoxicity of biodegradable Zn-Mg alloy [J]. J Biomed Mater Res B Appl Biomater, 2015, 103(8): 1632-1640

[17] Vojtech D, Kubasek J, Serak J, et al. Mechanical and corrosion properties of newly developed biodegradable Zn-based alloys for bone fixation[J]. Acta Biomater, 2011, 7(9): 3515-3522

[18] Yang H, Wang C, Liu C, et al. Evolution of the degradation mechanism of pure zinc stent in the one-year study of rabbit abdominal aorta model[J]. Biomaterials, 2017, 145: 92-105

[19] Bakhsheshi-Rad H R, Hamzah E, Low H T, et al. Fabrication of biodegradable Zn-Al-Mg alloy: Mechanical properties, corrosion behavior, cytotoxicity and antibacterial activities[J]. Mater Sci Eng C Mater Biol Appl, 2017, 73: 215-219

[20] Zhao Q M, Li G Z, Zhu H M, et al. Study on Effects of Titanium Surface Microporous Coatings Containing Zinc on Osteoblast Adhesion and Its Antibacterial Activity [J]. Appl Bionics Biomech, 2017, 2017: 2906575

[21] Shen X, Hu Y, Xu G, et al. Regulation of the biological functions of osteoblasts and bone formation by Zn-incorporated coating on microrough titanium [J]. ACS Appl Mater Interfaces, 2014, 6(18): 16426-16440

[22] Qiao Y, Zhang W, Tian P, et al. Stimulation of bone growth following zinc incorporation into biomaterials[J]. Biomaterials, 2014, 35(25): 6882-6897

(下转第 1888 页)

and safety of a peptide-based enteral formula versus a high protein enteral formula in multiple ICU settings (medical,surgical, cardiothoracic)[J]. Clin Nutr, 2017, 36(3): 706-709

[8] Liu Bin, Bin Wen-kai, Chen Xiao-mei, et al. A Meta-analysis of Clinical Effcacy for Enteral Nutrition vs Parenteral Nutrition in Critical illness[J]. Parenteral & Enteral Nutrition, 2017, 24(5): 277-282

[9] Poulia K A, Klek S, Doundoulakis I, et al. The two most popular malnutrition screening tools in the light of the new ESPEN consensus definition of the diagnostic criteria for malnutrition [J]. Clin Nutr, 2017, 36(4): 1130-1135

[10] Lew C, Yandell R, Fraser R, et al. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review [J]. JPEN J Parenter Enteral Nutr, 2017, 41(5): 744-758

[11] Reintam B A, Malbrain M L, Starkopf J, et al. Gastrointestinal function in intensive care patients: terminology, definitions and management Recommendations of the ESICM Working Group on Abdominal Problems [J]. Intensive Care Med, 2012, 38(3): 384-394

[12] Hart G K, Dobb G J. Effect of a fecal bulking agent on diarrhea during enteral feeding in the critically ill [J]. JPEN J, 1988, 12(5): 465-468

[13] Kirkpatrick A W, Roberts D J, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome [J]. Intensive Care Med, 2013, 39(7): 1190-1206

[14] Su Heyi, Mo Zexun, Chen Zhen, et al. Severe immune imbalance in ICU-persistent inflammation- immunosuppressive-decomposition metabolic syndrome[J]. Chinese Critical Care Medicine, 2017, 24 (8): 760-764

[15] Meng Pengfei, Ren Zhiqiang, Zhang Dingcheng, et al. Effect of acrylamide glutamine combined with early enteral nutrition support on patients with severe pancreatitis in ICU[J]. China Clinical Practical Medicine, 2018, 9(2): 43-45

[16] Jiang Ming, Wan Nianliang, Li Bo, et al. Effect of enteral nutrition support through nasal jejunum on prognosis of patients with acute craniocerebral trauma in ICU mechanical ventilation [J]. Modern Journal of Integrated Traditional Chinese and Western Medicine, 2016, 25(25): 2818-2821

[17] Cartin-Ceba R, Afessa B, Gajic O. Low baseline serum creatinine concentration predicts mortality in critically ill patients independent of body mass index[J]. Crit Care Med, 2007, 35(10): 2420-2423

[18] Li Ting, Bai Yunhui, Zhang Yunsong, et al. Evaluation of Nutritional Therapy in Patients with Different Diseases [J]. Labeled Immunoassays and Clinical Medicine, 2016, 23(3): 297-299

[19] Yan Zheng, Huang Yingzi, Lv Guozhong, et al. Correlation between influencing factors and prognosis of enteral nutrition intolerance in severely burned patients[J]. Guangdong Medical Journal, 2016, 37(4): 567-569

[20] Moro K, Koyama Y, Kosugi S I, et al. Low fat-containing elemental formula is effective for postoperative recovery and potentially useful for preventing chyle leak during postoperative early enteral nutrition after esophagectomy[J]. Clin Nutr, 2016, 35(6): 1423-1428

[21] Pugh JN, Sage S, Hutson M, et al. Glutamine supplementation reduces markers of intestinal permeability during running in the heat in a dose-dependent manner [J]. Eur J Appl Physiol, 2017, 117(12): 2569-2577

(上接第 1857 页)

[23] Liang D, Yang M, Guo B, et al. Zinc upregulates the expression of osteoprotegerin in mouse osteoblasts MC3T3-E1 through PKC/ MAPK pathways[J]. Biol Trace Elem Res, 2012, 146(3): 340-348

[24] Li H F, Xie X H, Zheng Y F, et al. Development of biodegradable Zn-1X binary alloys with nutrient alloying elements Mg, Ca and Sr [J]. Sci Rep, 2015, 5: 10719

[25] Tapiero H, Tew K D. Trace elements in human physiology and pathology: zinc and metallothioneins[J]. Biomed Pharmacother, 2003, 57(9): 399-411

[26] Festa M D, Anderson H L, Dowdy R P, et al. Effect of zinc intake on copper excretion and retention in men [J]. Am J Clin Nutr, 1985, 41 (2):285-292

[27] Fieten H, Hugen S, van den Ingh T S, et al. Urinary excretion of copper, zinc and iron with and without D-penicillamine administration in relation to hepatic copper concentration in dogs[J]. Vet J, 2013, 197(2): 468-473

[28] Foster M, Samman S. Zinc and Regulation of Inflammatory Cytokines: Implications for Cardiometabolic Disease [J]. Nutrients, 2012, 4(12): 676-694

[29] Guillory R J, Bowen P K, Hopkins S P, et al. Corrosion Characteristics Dictate the Long-Term Inflammatory Profile of Degradable Zinc Arterial Implants [J]. ACS Biomaterials Science & Engineering, 2016, 2(12): 2355-2364

[30] Prasad A S. Clinical, biochemical, and pharmacological role of zinc [J]. Annu Rev Pharmacol Toxicol, 1979, 19: 393-426

[31] Fosmire G J. Zinc toxicity[J]. Am. J. Clin. Nutr., 1990(51): 225-227

[32] Nriagu J. Zinc Toxicity in Humans [M]. Encyclopedia of Environmental Health. Burlington: Elsevier, 2011: 801-807

[33] King J C, Shames D M, Woodhouse L R. Zinc homeostasis in humans[J]. J Nutr, 2000, 130(5S Suppl): 1360S-1366S