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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 *

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摘要 目的:探讨新型可降解锌合金内固定系统用于犬下颌骨骨折固定的可行性。**方法:**选择比格犬 12 只,并将其随机分为两组,其中 6 只为锌合金实验组,6 只为钛合金对照组。每只比格犬的下颌作左右两个骨折内固定模型,每侧骨折模型使用一套小型四孔直连内固定产品。分别于术后即刻、术后 4 周、12 周拍 X 片。于术前、术后 4 周、12 周、24 周抽血检测微量元素锌。于术后 12 周、24 周分批将动物安乐死,取下颌骨块行 Micro-CT 检测,取动物重要脏器和内固定周围软组织做病理切片。**结果:**全程动物无脱落,实验组与对照组骨折均临床愈合。X 线图像及 Micro-CT 显示实验组与对照组的内固定效果比较差异无统计学意义($P>0.05$)。锌合金表面有明显的降解产物, Micro-CT 测量锌合金的板钉初始体积为 $155.8 \pm 1.536 \text{ mm}^3$, 12 周体积为 $147.1 \pm 0.9893 \text{ mm}^3$, 24 周体积为 $137 \pm 5.365 \text{ mm}^3$, 降解率 12.07%, 随着植入后时间的延长显著下降($P<0.05$), 而钛合金板钉体积无显著变化。实验组及对照组心、肝、肾及植入物周围软组织均未见异常。血清锌离子浓度在正常范围内略有上升, 各时间节点比较差异无统计学意义($P>0.05$)。**结论:**可降解锌合金内固定系统可以对犬下颌骨骨折提供稳固的固定, 可降解锌合金在下颌骨部位具有一定的降解性能, 血液中锌离子未见明显异常升高, 对心、肝、肾及植入物周围软组织无毒性作用。

关键词: 锌; 合金; 可降解; 骨折固定术; 下颌骨

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A Study on a New Type of Biodegradable Zinc Alloy Internal Fixation System for Mandibular Fracture Fixation in Dogs*

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ABSTRACT Objective: To explore the feasibility of internal fixation system prepared by the new biodegradable zinc alloy for the fixation of mandibular fractures in dogs. **Methods:** Twelve beagle dogs were selected and randomly divided into two groups with 6 cases in each group, zinc alloy experimental group and titanium alloy control group. Each beagle dog mandibular made of left and right fracture fixation model, each side of the fracture model was treated by a small four-hole direct internal fixation products. The radiographs was taken immediately after operation, at 4 weeks and 12 weeks after operation. Zn content in blood plasma was measured preoperation, at 4 weeks, 12 weeks and 24 weeks after operation. Animals were euthanized at 12 weeks and 24 weeks. Micro-CT was performed on the mandible of canine. The vital organs of animals and the soft tissue surrounding the internal fixation were used for pathological sections. **Results:** The animals in experimental group and control group were clinically healed. X-ray images and Micro-CT showed no significant difference in the effect of fixation between two groups($P>0.05$). Zinc alloy surface showed obvious degradation products. The initial volume of zinc alloy plate and nails measured with Micro-CT was $155.8 \pm 1.536 \text{ mm}^3$, the volume at 12 weeks was $147.1 \pm 0.9893 \text{ mm}^3$, the volume at 24 weeks was $137 \pm 5.365 \text{ mm}^3$, the degradation rate was 12.07%, which decreased significantly with the prolongation of time after implantation ($P<0.05$), while the volume of titanium alloy plate and nails showed no significant change. There was no abnormalities in the soft tissue of heart, liver, kidney and soft tissue surrounding the internal fixation in the experimental group and the control group. Serum zinc ion concentration in the normal range of a slight increase, there was no significant difference between each time point($P>0.05$). **Conclusion:** Degradable zinc alloy internal fixation system can provide a solid fixation for canine mandibular fractures. Degradable

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zinc alloy has a certain degradation performance in the mandible of the canine. There was no significant abnormally high increase in zinc concentration in the blood. Degradable zinc alloy has no toxic effect on the heart, liver, kidney and the soft tissue surrounding the internal fixation.

Key words: Zinc; Alloy; Biodegradable; Fracture Fixation; Mandible

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前言

目前,钛合金是最常用的内固定材料,由于其与骨皮质间存在应力遮挡效应^[1],长时间就会造成骨质疏松,甚至取板后的再骨折^[2]。生物可降解高分子材料可以降解,由于其强度不足,降解产物为酸性,导致无菌炎症,影响骨的修复愈合的问题限制了其应用^[3]。而早在上世纪,可降解镁合金就被引入骨科领域,但是由于其降解过快,产生氢气等因素,故未能推广^[4,5]。

可降解锌合金是一种全新材料,具有充足的强度、良好的组织相容性和可塑性,最重要是可以降解^[6]。由于其降解速率相对缓慢,可以在体内发挥足够长的时间,成为最近的研究热点^[7-13]。本研究采用的课题组发明专利——一种人体可降解的耐蚀高强韧 Zn、Fe、RE 系锌合金^[14]包括 Zn、Fe 和 RE 元素,其中 Zn 元素的质量百分含量为 82~99.997%,Fe 元素的质量百分含量为 0.002~10%,RE 元素的质量百分含量为 0.001~8%。由其所制备的内固定系统,经体外测试具有良好的力学性能。同时体外实验证明该材料细胞相容性良好,细胞毒性检测合格,其表面能被细胞黏附生长;另外具有抗菌性能,可以抑制大肠杆菌和金黄色葡萄球菌^[15]。本研究主要探讨了可降解锌合金制备的内固定系统用于动物下颌骨骨折治疗的可行性。

1 材料与方法

1.1 试验材料

试验组:四孔直连可吸收锌合金接骨板和接骨螺钉(陕西春晖百奥医疗科技有限责任公司设计并提供)。对照组:已上市的四孔直连钛合金接骨板和接骨螺钉(西安中邦钛生物材料有限公司提供)。试验组和对照组型号规格均为:四孔直连接骨板板厚 δ 1.0 mm,接骨螺钉 Φ 2.0 mm $\times$ 7 mm。产品均经环氧乙烷灭菌消毒,无菌袋封装备用。(图 1)。



图 1 实验组(A)与对照组(B)接骨装置

Fig.1 Experimental group (A) and Control group (B) bone device

1.2 试验动物及分组

健康成年比格犬 12 只,体重 10~12 kg,狗龄 10~12 个月,雌雄各半。骨龄发育成熟,无头颈部外伤。所有试验动物均由第四军医大学口腔医院动物实验中心购买提供。动物实验方案经第四军医大学口腔医院动物伦理委员会批准,中国食品药

品检定研究院授权,依据中华人民共和国科学技术部颁发的《关于善待实验动物的指导意见》,实验过程中对动物的处理符合动物伦理学要求,在第四军医大学口腔医院动物实验中心进行(许可证号 SYXK(军)2015-0001)。

将 12 只比格犬随机分为两组,其中 6 只为锌合金实验组,6 只为钛合金对照组。每只比格犬的下颌作左右两个骨折内固定模型,每侧骨折模型使用一套小型四孔直连内固定产品,共有 24 个下颌骨骨折模型。

1.3 下颌骨骨折模型的建立

比格犬术前均禁食 12 h,禁水 4 h。动物称重后,于术前 30 分钟用阿托品 0.5 mL/只肌内注射,青霉素 G 钠 80 万单位肌肉注射。随后用速眠新 II 0.1 mL/kg 肌内注射诱导麻醉,3%戊巴比妥钠 0.3 mL/kg 肌注注射加强。麻醉起效后,动物采取仰卧位。四肢固定。剃毛,拉出舌头并妥善固定。常规消毒、手术铺巾,利多卡因(含 1/20 万肾上腺素)行局部浸润麻醉。沿犬下颌骨下缘略偏内侧切开皮肤、皮下组织,钝性分离口底肌群至下颌骨骨膜,沿下颌骨下缘切开骨膜,翻瓣暴露下颌骨。在犬下颌第四前臼齿和第一臼齿之间、垂直于下颌骨下缘定位截骨线,用来复锯在喷水冷却条件下切割颊、舌侧骨皮质,并注意保护下领管中的血管神经。切开皮质骨后,取一块四孔小型接骨板塑形,随之以骨折内固定的方式置于截骨线两侧。取高速电钻,转头直径为 1.7 mm,在小型四孔板内钻孔,攻丝后拧入直径为 2.0 mm、长度为 7 mm 的螺钉。旋出螺钉,取出内固定板,于截骨线处用骨凿凿开造成下颌骨线形骨折并充分分离骨折断端。凿断下颌骨前先把内固定板定位,可以避免凿开后下颌骨的错误移位,防止咬合关系的错乱,更好的保证实验的一致性。手法充分复位后,取已定位的一块四孔小型接骨板及四颗单皮质螺钉,按照已有的钻孔行坚固固定术。完成一侧下颌骨骨折模型后,按照同样的方法行另一侧下颌骨骨折模型的建立。取大量生理盐水冲洗伤口,充分止血,分层缝合伤口(图 2)。术后当即拍片。术后动物单独饲养,肌注青霉素 3 天,半流食两周。



图 2 截骨造成下颌骨线形骨折(A),可降解锌合金内固定系统固定后效果(B)

Fig.2 Osteotomy manufacturing mandibular linear fractures (A), The fixing effect of the biodegradable zinc alloy internal fixation system (B)

1.4 大体观察

术中观察三组内固定材料的强度,固定效果。手术结束对

动物进行观察、饲养,应观察实验动物的进食、饮水、活动情况,检查伤口愈合情况、局部组织反应。于术后 12 周、24 周将动物采用静脉注入过量麻醉安乐死,解剖下颌骨并观察骨折线愈合情况。取电锯锯开制备成双侧下颌骨骨折动物模型。肉眼观察观察植入物周围软组织有无炎症等组织反应,观察植入物表面形态变化并拍照记录。

1.5 活体血液微量元素锌检查及 X 线检查

分别于术前、术后 4 周、12 周、24 周这四个时间活体抽血检测血液微量元素锌;于术后即刻、术后 4 周、12 周拍 X 片检测骨折愈合。

1.6 Micro-CT 检查

术后 12 周、24 周动物安乐死后,取动物下颌骨内固定骨块行 Micro-CT 检查(德国 Y.Cheetah 微米 X 射线三维成像系统),观察骨折的愈合情况和植入物的固定情况。同时用 VG Studio2.2 软件分析骨折断端处的骨体积分数(BV/TV)、骨小梁厚度(Tb.Th)、骨小梁数量(Tb.N)、骨表面积与体积比(BS/BV)、骨小梁分离度(Tb.Sp),并同时分析锌合金板和钉的残余体积。

1.7 组织学检查

动物安乐死后,取动物心脏、肝脏、肾脏及内固定植入物的周围软组织固定于 4%甲醛中,制作成病理切片,采用 HE 染色观察组织形态。

1.8 统计学分析

采用 SPSS22.0 统计软件进行统计学分析,多组间计量资料的比较采用 t 检验和单因素方差分析,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

动物术后 30 分钟苏醒,精神萎靡,无食欲。1 d 后精神恢复,进食半流食基本正常。2 周后改为进食普食,动物能够顺利咀嚼,未观察到进食困难。锌合金内固定组植入区伤口均为一期愈合,创口无红肿、溢脓、瘻道、露板等出现。未观察到诸如过敏等二次反应。未观察到局部产气现象。参加实验的 12 只比格犬,中途无脱落。钛合金组出现一例术后 7 日伤口感染,经抗感染治疗 3 日后,伤口愈合。

2.2 锌合金内固定系统在体内的降解性能

动物处死后,解剖下颌骨,植入的锌合金内固定接骨板和螺钉未见松动脱落,锌合金内固定表面可见颗粒状降解物,且随着时间的增长,降解颗粒越多(图片 3A)。动物安乐死后,截取带有内固定装置的部分下颌骨骨端,行 Micro-CT 检查,并在 VG-studio2.2 软件中进行三维重建。我们利用锌合金与骨组织之间的密度差异,设置固定的灰度阈值,将锌合金内固定板、钉与犬下颌骨区分出来。Micro-CT 图像展示了 24 周的锌合金板钉的情况,可见锌合金板及螺钉表面出现明显的降解,并随着时间的增加而更加明显(图片 3B)。VG-studio2.2 软件提取的数据提供了更加精确的证据(图片 3C)。锌合金的板钉初始体积为 $155.8 \pm 1.536 \text{ mm}^3$,12 周体积为 $147.1 \pm 0.9893 \text{ mm}^3$ 。24 周体积为 $137 \pm 5.365 \text{ mm}^3$,降解率 12.07%。钛合金板钉体积无显著变化。

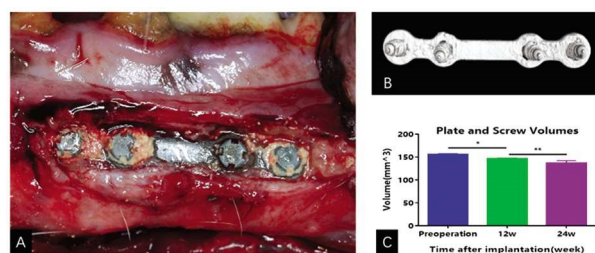


图 3 A、术后 24 周锌合金表面颗粒状降解物;B、Micro-CT 三维重建显示 24 周锌合金板及螺钉表面出现明显的降解;C、锌合金内固定板钉体积变化。* $P<0.05$;** $P<0.01$

Fig.3 A. After 24 weeks, the surface of the zinc alloy appeared granular degradation products. B. Three-dimensional reconstruction of Micro-CT showed significant degradation of zinc alloy plate and screw surface at 24 weeks. C. Volume change of zinc alloy internal fixation device. * $P<0.05$; ** $P<0.01$

2.3 锌合金内固定系统接骨有效性

2.3.1 X 线检查 术后 4 周后,锌合金组和钛合金组骨折间隙模糊。12 周后,锌合金和钛合金组骨折线密度进一步增高,模糊不清。骨折间隙中新生骨质均匀,皮质骨形成良好(图 4)。

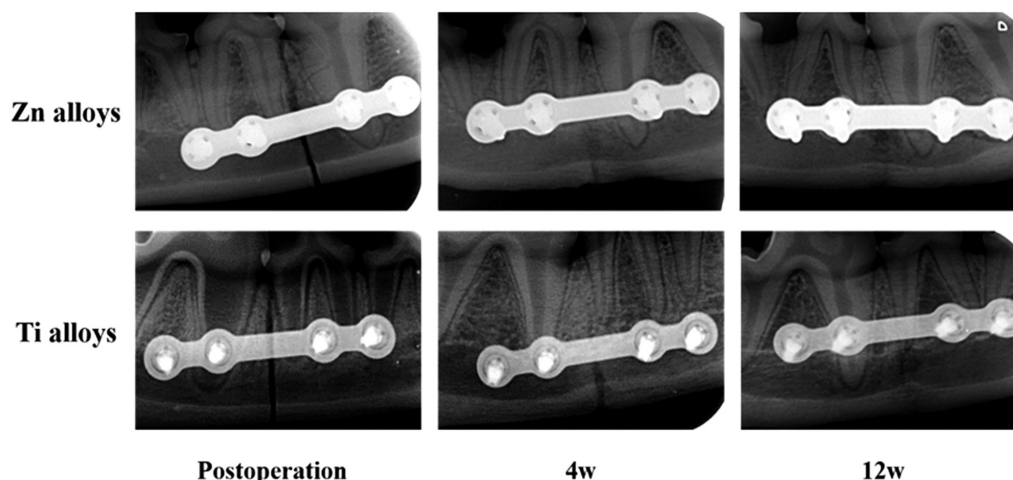


图 4 实验组与对照组内固定 X 线情况

Fig. 4 X-ray of the internal fixation of the experimental and control groups

2.3.2 Micro-CT 检查 Micro CT 图像展示了 24 周锌合金内固定下颌骨骨折愈合情况,本实验取下颌骨骨折处为中心设置一高 7 mm,宽 3 mm 兴趣区,将兴趣区设置黄色高亮(图 5A)。VG-Studio2.2 软件进一步分析并生成数据。在术后 12 周、24 周

这两个时间节点,实验组与对照组的 BV/TV、BS/BV、Tb.Th、Tb.N、Tb.Sp 比较差异均无明显统计学意义(图 5 B-F),表明实验组与对照组的接骨有效性无明显差异。

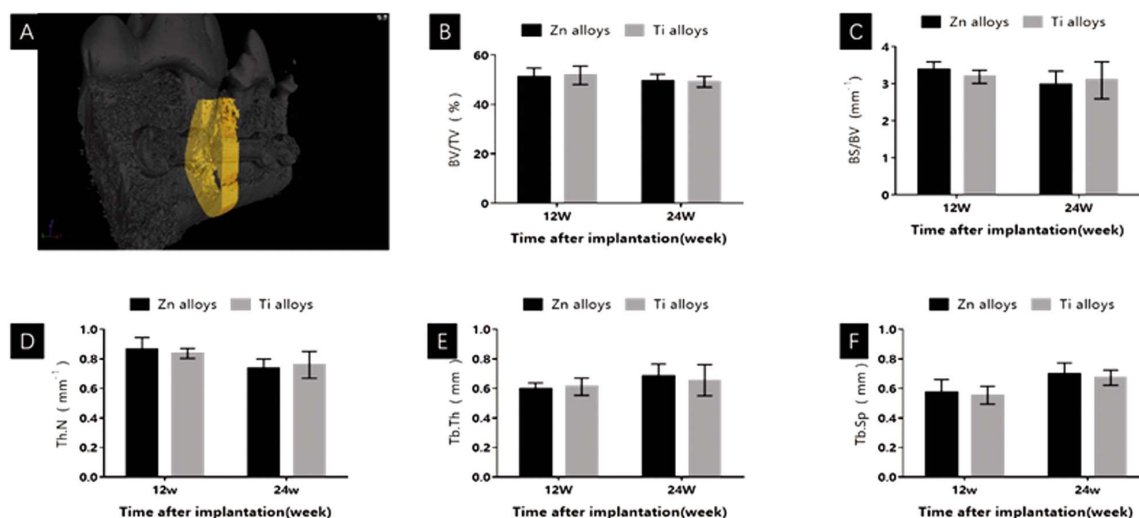


图 5 术后 12 周、24 周实验组下颌骨骨折愈合情况及选取的黄色高亮兴趣区(A)。获取数据并绘制骨愈合相关指标(B-F)

Fig.5 12 weeks, 24 weeks after surgery, the healing of mandibular fractures in the experimental group and the yellow highlight area were selected(A).

Obtain data and draw the relevant indicators of bone healing (B-F)

2.4 锌合金内固定体内安全性及生物相容性

实验期间,两组动物精神无萎靡,进食正常,大小便无异常,眼耳口鼻无异常分泌物,皮毛有光泽、无异常脱落,实验后体重略有增加。

2.4.1 组织学检查 为了评估锌合金体内的相容性,本实验取

植入物板周软组织分析局部细胞毒性,取心脏、肝脏、肾脏分析全身细胞毒性。通过显微镜观察,内固定植入术后 24 周的实验组及对照组板周软组织未见炎性细胞浸润。心、肝、肾未见明显形态改变,未见炎症细胞浸润,肝肾未见有害物质积蓄(图 6)。

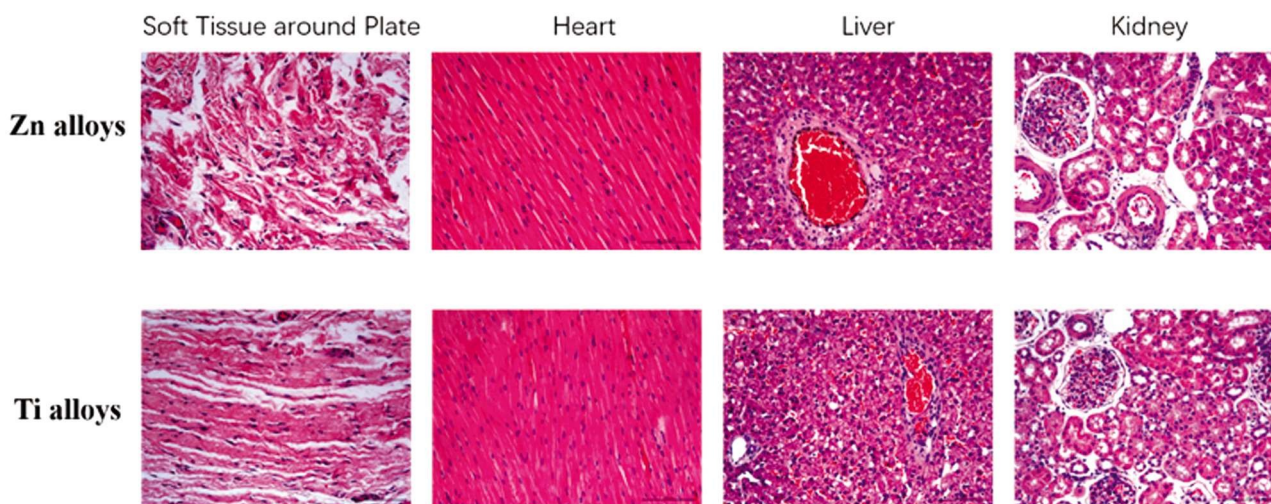


图 6 术后 24 周,实验组与对照组的 H-E 染色情况。图片选取动物的内固定板周软组织、心脏、肝脏、肾脏组织

Fig.6 24 weeks after surgery, experimental group and control group H-E staining. Picture Select the soft tissue around the internal fixation plate, heart, liver, kidney tissue

2.4.2 血清锌离子浓度 血清锌离子浓度在正常范围内略有上升,各时间节点比较差异未见统计学意义(图 7)。

3 讨论

锌是人体必需的微量元素之一。近年来关于新型医用可降解锌合金的研究越来越多^[7,16-18]。相关研究发现锌合金降解速率

相对缓慢,和镁基材料相比,可以更好地满足生物力学需求^[19]。另外,锌具有抗菌性能,有不易耐药、抗菌持久的优势^[20]。研发具有抗菌性能的植入物可以减少临床上植入物感染和取出^[21]。

本研究采用课题组发明专利 -- 医用可降解锌合金,将其制备成适合颌面部用的内固定板和螺钉,在体外测试其材料强度、柔韧性、硬度,以及制造成螺钉的旋转扭矩、旋转角度等物

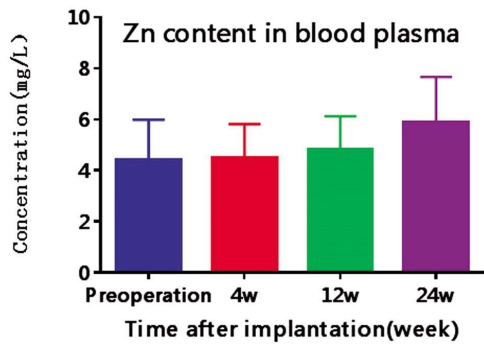


图 7 血清锌离子浓度的变化

Fig.7 Changes of serum zinc ion concentration

理指标都是符合临床需求的。植入大动物体内后,固定骨折模型的效果良好。X 片和 Micro-CT 均观察到实验组的皮质骨均形成较好,骨小梁分布均匀,骨小梁粗细基本一致。植入后 12 周、24 周,实验组与对照组的 BV/TV、BS/BV、Tb.Th、Tb.N、Tb.Sp 均无明显差异,说明实验组与对照组的接骨有效性无明显差异。

良好的生物相容性是植入物的基本要求,相关的体外实验证明锌合金具有良好的细胞相容性,细胞毒性安全合格,没有致突变性和遗传毒性^[7,8,15]。在本实验中,我们观察到实验动物比格犬全身状况无异常变化,植入物周围软组织及心脏、肝脏、肾脏的组织病理学未见有改变,初步说明锌合金材料应该具备良好的组织相容性。同时,血液中锌离子浓度变化缓慢,在正常的生理范围内呈现一种逐渐上升的趋势,但升高的数值较前比较无统计学差异。术后 4 周锌离子浓度基本没有变化,但术后 12 周锌离子浓度升高变快,可能的原因是锌合金初始降解速度较慢,12 周后植入物表面崩解后,降解加快有关。至于随着锌合金内固定材料的进一步降解,锌离子浓度会不会继续升高,本实验相关的降解及生物相容性动物实验仍在进行中,血常规及血生化等指标我们亦会在后续的试验中总结。

均匀的生物降解行为对可降解的内固定植入物至关重要,因为不均匀的降解导致局部应力集中,可能会意外的早期破坏,失去内固定的效果。相关体外实验证实锌合金相对于镁合金的主要优势是在体液中的较高的耐腐蚀性和较慢的降解速度^[7,9]。本实验从动物实验方面进一步证明了锌合金具有较高的耐腐蚀性和较慢的降解速度,术后 12 周锌合金内固定板钉表面均匀腐蚀,内固定表面可见颗粒状降解物,仍具有完整的形态,局部未观察到有气体产生。由于本实验观察时间不够长,后期锌合金的降解曲线以及何时能最终降解完成,降解产物最终能否被身体代谢等问题暂时无法得知,在后续的研究中会进一步完善。

总之,由可降解锌合金制备的内固定系统可对犬下颌骨折提供稳固的固定,在下颌骨部位具有一定的降解性能,血液中锌离子未见明显异常升高,对心、肝、肾及植入物周围软组织无毒性作用。

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