Protein

Synergistic cardioprotective effects of rAAV9-CyclinA2 combined with fibrin glue in rats after myocardial infarction.

Authors: Cao W., Chang Y.-F., Zhao A.-C., Chen B.-D., Liu F., Ma Y.-T., Ma X.

Publication Date: 2017

PMID: 616956712

Abstract

The present study aimed to investigate the protective effects of rAAV9-CyclinA2 combined with fibrin glue (FG) in vivo in rats after myocardial infarction (MI). Ninety male Sprague-Dawley rats were randomized into 6 groups (15 in each group): sham, MI, rAAV9-green fluorescent protein (GFP) + MI, rAAV9-CyclinA2 + MI, FG + MI, and rAAV9-CyclinA2 + FG + MI. Packed virus (5 x 10^{11}vg/ml) in 150 micro l of normal saline or FG was injected into the infarcted myocardium at five locations in rAAV9-GFP + MI, rAAV9-CyclinA2 + MI, and rAAV9-CyclinA2 + FG + MI groups. The sham, MI, and FG + MI groups were injected with an equal volume of normal saline or FG at the same sites. Five weeks after injection, echocardiography was performed to evaluate the left ventricular function. The expressions of CyclinA2, proliferating cell nuclear antigen (PCNA), and phospho-histone-H3 (H3P), vascular density, and infarct area were assessed by Western blot, immunohistochemistry, immunofluorescence, and Masson staining. As a result, the combination of rAAV9-CyclinA2 and FG increased ejection fraction and fractional shortening compared with FG or rAAV9-CyclinA2 alone. The expression level of CyclinA2 was significantly higher in the rAAV9-CyclinA2 + FG + MI group compared with the rAAV9-CyclinA2 + MI and FG + MI groups (70.1 +/- 1.86% vs. 14.74 +/- 2.02%, $P < 0.01$; or vs. 50.13 +/- 3.80%; $P < 0.01$). A higher expression level of PCNA and H3P was found in the rAAV9-CyclinA2 + FG + MI group compared with other groups. Comparing with other experiment groups, collagen deposition and the infarct size significantly decreased in rAAV9-CyclinA2 + Fibrin + MI group. The vascular density was much higher in the rAAV9-CyclinA2 + FG + MI group compared with the rAAV9-CyclinA2 + MI group. We concluded that fibrin glue combined with rAAV9-CyclinA2 was found to be effective in cardiac remodeling and improving myocardial protection.

Full Text

Delivery of AAV9cyclin-A2 via fibrin glue induces cardiac regeneration as well as improves cardiac function in vivo post myocardial infarction.

Authors: Wen C., Ma Y., Ma X.

Publication Date: 2014

PMID: 71664178

Abstract

Objectives: To assess the effects of exogenousCyclin-A2 with Fibrin glue in vivo post MI. Methods: Seventy-two male Sprague Dawleyrats were randomly divided into six groups: Sham (n=12); MI+PBS (n=12); MI+GFP (n=12); MI+Fibrin (n=12); MI+AAV9Cyclin-A2 (n=12); MI+Fibrin +AAV-9Cyclin-A2 (n=12). $5x10^{11}$ genome copies in PBS or Fibrin were injected into the infarcted myocardium at three different points around the infarcted regions. Echocardiography was performed to assess the left ventricular function. The hearts of each group were harvested four weeks post MI to assess gene expression, apoptosis, vascular density, infarct areaby Western Blot, immunohistochemistry and Masson Triple Stain. Results: The Western Blot expression of Cyclin A2 and PCNA were significantly higher in MI+Fibrin +AAV-9Cyclin-A2 than those found in two other control groups (MI+AAV9Cyclin-A2 and MI+Fibrin) (P< 0.01). However, mitosis specific protein, H3P and Aurora B had no statistical difference among six groups (F=5,P>0.05). Strikingly, sequential delivery of AAV9Cyclin-A2 increased EF compared with PBS alone (F=18,P<0.05) or Fibrin blank (F=32,P<0.01), but no significant difference in the LVESD was observed between the six groups. Meanwhile, the values of EF were: Sham (82.81+/-2.37) %;MI+PBS (38.78+/-4.59) %;MI+GFP (38.78+/-4.59) %; MI+Fibrin (56.88+/-4.07) %; MI+AAV9Cyclin-A2 (70.57+/-3.76) %; MI+Fibrin +AAV- 9Cyclin-A2 (75.37+/-4.69) % respectively. Comparing with other groups, fibrosis and the infarct size significantly decreased in MI+Fibrin +AAV-9Cyclin-Agroup. Vascular density were significantly higher in MI+Fibrin +AAV-9Cyclin-A2group except the Sham group than other four groups. Conclusions: AAV9Cyclin-A2 with Fibrin serve as a new approach in cardiac remodeling as well as promoting cardiomyocytes regeneration and vascular density. This new method paves the way for novel interventional approaches to myocardial repair, using both Adeno-associated virus and matrices.

Full Text

Revascularization of rat fasciocutaneous flap using CROSSEAL with VEGF protein or plasmid DNA expressing VEGF.

Authors: McKnight C.D., Winn S.R., Gong X., Hansen J.E., Wax M.K.

Publication Date: 2008

PMID: 352010406

Abstract

Background: Fasciocutaneous tissue transfer is a common reconstructive procedure. Revascularization of flap tissue is an important component of tissue healing. Gene therapy offers an avenue through which the period of pedicle vascular dependency can be reduced. Materials and Methods: Rat fasciocutaneous flaps were elevated and a two-hour ischemic time induced. Polycation complex (jet

PEI) and human fibrin sealant CROSSEAL was applied between flap and underlying abdominal tissues. Group 1 (six rats) was the control; Group 2 (seven rats) had vascular endothelial growth factor (VEGF) protein applied; Group 3 (seven rats) had plasmid DNA expressing VEGF applied. Vascular pedicles were ligated on postoperative day 5, percentage flap survival evaluated on day 7. Results: All flaps survived initial ischemia. Mean +/- SD percentage area of the flap that survived was 28.1 +/- 12.4 (Group 1), 71.6 +/- 16.2 (Group 2), and 77.5 +/- 12.7 (Group 3) ($P < 0.001$, Group 1-3, 2-3). No differences were observed between Groups 2 and 3. Conclusions: Locally administered VEGF protein or plasmid DNA expressing VEGF enhanced survival of fasciocutaneous flaps.

Full Text

Transplantation of neonatal cardiomyocytes plus fibrin sealant restores myocardial function in a rat model of myocardial infarction.

Authors: Li Y.-S., Gao B.-R.

Publication Date: 2007

PMID: 350237811

Abstract

Background: Most cardiac regenerative approaches can restore injured heart muscles. In this study, we investigated if fibrin sealant could help neonatal cardiomyocytes restore myocardial function in a rat model of myocardial infarction. Methods: The left anterior descending artery in adult female Sprague-Dawley (SD) rats was ligated to make a myocardial infarction model. Neonatal ventricular cardiomyocytes from one-day male SD rats were isolated, labeled and cultured. The cells were injected into the infarcted area three weeks later. The animals were randomized into four recipient groups: (1) cardiomyocytes plus fibrin sealant (group CF, n=10); (2) cardiomyocytes alone (group C, n=10); (3) fibrin sealant recipients alone (group F, n=10); (4) control group (n=10). Four weeks after transplantation, echocardiography and Langerdoff model were used to assess heart function. Immunohistochemical staining and polymerase chain reaction (PCR) were performed to track the implanted cardiomyocytes and detect the sex-determining region Y gene on Y chromosome. Results: Echocardiography showed the fraction shortening (FS) in groups CF, C, F and control group was (27.80+/-6.32)%, (22.29+/-4.54)%, (19.24+/-6.29)% and (20.36+/-3.29)% respectively with statistically significant differences in group CF compared with the other groups ($P<0.05$). The Langendoff model revealed that the left ventricular development of peak pressure (LVDPmax, mmHg) in groups CF, C, F and control group was 104.81+/-17.05, 80.97+/-21.60, 72.07+/-26.17 and 71.42+/-17.55 respectively with statistically significant differences in group CF compared with the other groups ($P<0.05$). Pathological examination and PCR indicated that transplanted cardiomyocytes in group CF survived better than those in the other groups. Conclusion: Transplanted neonatal cardiomyocytes plus fibrin sealant can survive in myocardial infarctioned area and improve heart function greatly in rat models.

Full Text

Multiple uses of fibrin sealant for nervous system treatment following injury and disease.

Authors: Biscola N.P., Cartarozzi L.P., Ulian-Benitez S., Barbizan R., Castro M.V., Spejo A.B., Ferreira R.S., Barraviera B., Oliveira A.L.R.

Publication Date: 2017

PMID: 614752489

Abstract

Lesions to the nervous system often produce hemorrhage and tissue loss that are difficult, if not impossible, to repair. Therefore, scar formation, inflammation and cavitation take place, expanding the lesion epicenter. This significantly worsens the patient conditions and impairment, increasing neuronal loss and glial reaction, which in turn further decreases the chances of a positive outcome. The possibility of using hemostatic substances that also function as a scaffold, such as the fibrin sealant, reduces surgical time and improve postoperative recovery. To date, several studies have demonstrated that human blood derived fibrin sealant produces positive effects in different interventions, becoming an efficient alternative to suturing. To provide an alternative to homologous fibrin sealants, the Center for the Study of Venoms and Venomous Animals (CEVAP, Brazil) has proposed a new bioproduct composed of certified animal components, including a thrombin-like enzyme obtained from snake venom and bubaline fibrinogen. Thus, the present review brings up to date literature assessment on the use of fibrin sealant for nervous system repair and positions the new heterologous bioproduct from CEVAP as an alternative to the commercial counterparts. In this way, clinical and pre-clinical data are discussed in different topics, ranging from central nervous system to peripheral nervous system applications, specifying positive results as well as future enhancements that are necessary for improving the use of fibrin sealant therapy.

Full Text

ADSCs in a fibrin matrix enhance nerve regeneration after epineural suturing in a rat model.

Authors: Reichenberger M.A., Mueller W., Hartmann J., Diehm Y., Lass U., Koellensperger E., Leimer U., Germann G., Fischer S.

Publication Date: 2016

PMID: 612264941

Abstract

Background: Due to their unique properties, adipose derived stem cells (ADSCs) obtain promising potential to enhance nerve regeneration. The aim of this study was to investigate if fibrin-glue embedded ADSCs were a beneficial adjunct to primary coaptation in a rat sciatic nerve model. Materials and methods: Fifty male Lewis rats underwent sciatic nerve transection and subsequent epineural suture repair. The treatment group received ADSCs re-suspended in fibrin glue, while the control group received fibrin glue only. After 7, 21, 35, and 63 days, analysis involved axon count, myelin sheath thickness as well as N- and G-ratios. Additionally, muscle weight quotient (operated vs. non-operated site of the same animal) was calculated and compared between treatment and control groups. For co-detection of vital ADSCs, vessel walls, and Schwann cells, immunolabeling was performed with CM-DiI, SMA, and S-100 antibodies, respectively. Results: ADSCs led to a significant increase of myelinization at day 21 (0.508 +/- 0.085 mum vs. 0.381 +/- 0.044 mum, P = 0.025) and day 35 (0.872 +/- 0.09 micro m vs. 0.495 +/- 0.078 micro m; P = 0.01) after surgery. Axon count was significantly increased at day 21 (420 +/- 119 vs. 129 +/- 63; P = 0.003) and day 63 (284 +/- 137 vs. 111 +/- 26; P = 0.046) after surgery. N- and G-ratios were significantly different compared with control indicating enhanced nerve regeneration due to ADSC treatment at each time point (P < 0.05). Muscle weight quotient was significantly higher in the treatment group compared with the control at day 21 (44.01% +/- 6.16% vs. 35.03% +/- 2.61%; P = 0.014) and day 63 (65.49% +/- 2.81% vs. 58.79% +/- 4.06%; P = 0.009) after surgery. Co-detection of immunolabeled cells showed vital ADSCs at the neuronal repair site and in close proximity to intraneuronal vessels indicating active participation of ADSCs in the process of nerve regeneration and associated angiogenesis. Conclusion: ADSCs embedded in a fibrin matrix can significantly enhance regeneration of peripheral nerve injuries after primary coaptation. © 2015 Wiley Periodicals, Inc. Microsurgery 36:491-500, 2016. Copyright © 2015 Wiley Periodicals, Inc.

Full Text

Fibrin glue repair leads to enhanced axonal elongation during early peripheral nerve regeneration in an in vivo mouse model.

Authors: Koulaxouzidis G., Reim G., Witzel C.

Publication Date: 2015

PMID: 605451996

Abstract

Microsurgical suturing is the gold standard of nerve coaptation. Although literature on the usefulness of fibrin glue as an alternative is becoming increasingly available, it remains contradictory. Furthermore, no data exist on how both repair methods might influence the morphological aspects (arborization; branching) of early peripheral nerve regeneration. We used the sciatic nerve transplantation model in thy-1 yellow fluorescent protein mice (YFP; n = 10). Pieces of nerve (1cm) were grafted from YFP-negative mice (n = 10) into those expressing YFP. We performed microsuture coaptations on one side and used fibrin glue for repair on the contralateral side. Seven days after grafting, the regeneration distance, the percentage of regenerating and arborizing axons, the number of branches per axon, the coaptation failure rate, the gap size at the repair site and the time needed for surgical repair were all

investigated. Fibrin glue repair resulted in regenerating axons travelling further into the distal nerve. It also increased the percentage of arborizing axons. No coaptation failure was detected. Gap sizes were comparable in both groups. Fibrin glue significantly reduced surgical repair time. The increase in regeneration distance, even after the short period of time, is in line with the results of others that showed faster axonal regeneration after fibrin glue repair. The increase in arborizing axons could be another explanation for better functional and electrophysiological results after fibrin glue repair. Fibrin glue nerve coaptation seems to be a promising alternative to microsuture repair.

Full Text

Postmarketing safety of biologics and biological devices.

Authors: Woo E.J.

Publication Date: 2014

PMID: 372450764

Abstract

Background context Regardless of study design, the approval process of biologics and biological devices cannot identify every possible safety concern. Postmarketing safety surveillance can provide information based on real-world use of medical products in heterogeneous populations and is critical for identifying potentially serious adverse events, events that are too rare to be detected during premarketing studies, late complications, and events involving individuals or uses that were not evaluated in clinical trials. Purpose To review why adverse event reporting is important and how the information is used, with emphasis on the points that are most applicable for surgeons and other spine professionals. Methods This is an overview of postmarketing safety surveillance. Results Review of adverse event reports has resulted in safety notifications, label changes, and publications regarding the safety of biologics and biological devices, such as the risk of airway compromise after the use of recombinant human bone morphogenetic protein in cervical spine fusion, the occurrence of a fatal air embolism after the use of a fibrin sealant that had been applied with a spray device, and infections after allograft transplantation of human tissues. Conclusions In light of the rapid development of new biologics, postmarketing surveillance is imperative for ensuring that these products are as safe as possible. By reporting adverse events, surgeons and other health care professionals play a key role in improving and refining our understanding of the safety of biologics. © 2014 Elsevier Inc. All rights reserved.

Full Text

Hemostasis and other benefits of fibrin sealants/glues in spine surgery beyond

cerebrospinal fluid leak repairs.

Authors: Epstein N.E.

Publication Date: 2014

PMID: 600322986

Abstract

Background: Fibrin sealants (FS)/glues (FG) are primarily utilized in spinal surgery to either strengthen repairs of elective (e.g., intradural tumors/pathology) or traumatic cerebrospinal fluid (CSF) fistulas. Here, additional roles/benefits of FS/FG in spine surgery are explored; these include increased hemostasis, reduction of scar, reduction of the risk of infection if impregnated with antibiotics, and its application to restrict diffusion and limit some of the major complications attributed to the controversial "off-label" use of bone morphogeneitc protein (rhBMP-2/INFUSE). Methods: We reviewed multiple studies, focusing not just on the utility of FS/FG in the treatment of CSF fistulas, but on its other applications. Results: FS/FG have been primarily used to supplement elective/traumatic dural closure in spinal surgery. However, FS/FG also contribute to; hemostasis, reducing intraoperative/postoperative bleeding/transfusion requirements, length of stay (LOS)/costs, reduced postoperative scar/radiculitis, and infection when impregnated with antibiotics. Nevertheless, one should seriously question whether FS/FG should be applied to prevent diffusion and limit major complications attributed to the "off-label" use of BMP/INFUSE (e.g., limit/prevent heterotopic ossification, dysphagia/respiratory decompensation, and new neurological deficits). Conclusions: FS/FG successfully supplement watertight dural closure following elective (e.g., intradural tumor) or traumatic CSF fistulas occurring during spinal surgery. Additional benefits include: intraoperative hemostasis with reduced postoperative drainage, reduced transfusion requirements, reduced LOS, cost, scar, and prophylaxis against infection (e.g., impregnated with antibiotics). However, one should seriously question whether FS/FG should be used to contain the diffusion of BMP/INFUSE and limit its complications when utilized "off-label".

Full Text

Antitumor effect of fibrin glue containing temozolomide against malignant glioma.

Authors: Anai S., Hide T., Takezaki T., Kuroda J.-I., Shinojima N., Makino K., Nakamura H., Yano S., Kuratsu J.-I.

Publication Date: 2014

PMID: 53117037

Abstract

Temozolomide (TMZ), used to treat glioblastoma and malignant glioma, induces autophagy, apoptosis and senescence in cancer cells. We investigated fibrin glue (FG) as a drug delivery system for the local administration of high-concentration TMZ aimed at preventing glioma recurrence. Our high-power liquid chromatography studies indicated that FG containing TMZ (TMZ-FG) manifested a sustained drug release potential. We prepared a subcutaneous tumor model by injecting groups of mice with three malignant glioma cell lines and examined the antitumor effect of TMZ-FG. We estimated the tumor volume and performed immunostaining and immunoblotting using antibodies to Ki-67, cleaved caspase 3, LC3 and p16. When FG sheets containing TMZ (TMZ-FGS) were inserted beneath the tumors, their growth was significantly suppressed. In mice treated with peroral TMZ plus TMZ-FGS the tumors tended to be smaller than in mice whose tumors were treated with TMZ-FGS or peroral TMZ alone. The TMZ-FGS induced autophagy, apoptosis and senescence in subcutaneous glioma tumor cells. To assess the safety of TMZ-FG for normal brain, we placed it directly on the brain of living mice and stained tissue sections obtained in the acute and chronic phase immunohistochemically. In both phases, TMZ-FG failed to severely damage normal brain tissue. TMZ-FG may represent a safe new drug delivery system with sustained drug release potential to treat malignant glioma.

Full Text

Motor Recovery and Synaptic Preservation after Ventral Root Avulsion and Repair with a Fibrin Sealant Derived from Snake Venom.

Authors: Barbizan R., Castro M.V., Rodrigues A.C., Barraviera B., Ferreira R.S., Oliveira A.L.R.

Publication Date: 2013

PMID: 368860075

Abstract

Background:Ventral root avulsion is an experimental model of proximal axonal injury at the central/peripheral nervous system interface that results in paralysis and poor clinical outcome after restorative surgery. Root reimplantation may decrease neuronal degeneration in such cases. We describe the use of a snake venom-derived fibrin sealant during surgical reconnection of avulsed roots at the spinal cord surface. The present work investigates the effects of this fibrin sealant on functional recovery, neuronal survival, synaptic plasticity, and glial reaction in the spinal motoneuron microenvironment after ventral root reimplantation.Methodology/Principal Findings:Female Lewis rats (7 weeks old) were subjected to VRA and root replantation. The animals were divided into two groups: 1) avulsion only and 2) replanted roots with fibrin sealant derived from snake venom. Post-surgical motor performance was evaluated using the CatWalk system twice a week for 12 weeks. The rats were sacrificed 12 weeks after surgery, and their lumbar intumescences were processed for motoneuron counting and immunohistochemistry (GFAP, Iba-1 and synaptophysin antisera). Array based qRT-PCR was used to evaluate gene regulation of several neurotrophic factors and receptors as well as inflammatory related molecules. The results indicated that the root reimplantation with fibrin sealant enhanced motor recovery, preserved the synaptic covering of the motoneurons and improved neuronal survival. The replanted group did not show significant changes in microglial response compared to

VRA-only. However, the astroglial reaction was significantly reduced in this group.Conclusions/Significance:In conclusion, the present data suggest that the repair of avulsed roots with snake venom fibrin glue at the exact point of detachment results in neuroprotection and preservation of the synaptic network at the microenvironment of the lesioned motoneurons. Also such procedure reduced the astroglial reaction and increased mRNA levels to neurotrophins and anti-inflammatory cytokines that may in turn, contribute to improving recovery of motor function.

Full Text

Clinical comparison between microporrus polysaccharide hemispheres (MPH) and fibrin glue during laparoscopic partial nephrectomy.

Authors: Makiyama K., Sakata R., Sano F., Yamanaka H., Nakaigawa N., Yao M., Kubota Y.

Publication Date: 2012

PMID: 70876261

Abstract

OBJECTIVE: Using hemostatic agents is one of the options to avoid complications during laparoscopic partial nephrectomy (LPN). Microporous polysaccharide hemispheres are made entirely from purified potato starch that activates the clotting cascade via a unique mechanism that hyperconcentrates platelets and coagulation proteins. We compare the efficacy of this new hemostatic agent, MPH and the standard hemostatic agent, fibrin glue. METHODS: Between January 2007 and October 2011, 70 LPNs with hilar clamping were completed by a single surgeon in Yokohama City University Hospital. We compare two sequential groups of patients: group A consisted of 27 patients in whom MPH was used and group B consisted of 43 patients in whom fibrin glue was used. These agents (MPH and fibrin glue) were applied to the partial nephrectomy bed before tying a suture in parenchymal suturing and after the renal hilum was unclamped. Study variables included blood loss, ischemic time and perioperative complications. RESULTS: Group A showed significantly less mean estimated blood loss (29.8 vs. 86.3 ml; p = 0.004) and less mean ischemic time (21.4 vs. 28.5 min; p = 0.002) than these of group B. Postoperative complications occurred in two patients in group B, but there were no postoperative complications in group A. CONCLUSIONS: MPH is available as an adequate hemostatic agent during LPN. There was no significant difference in the incidence of postoperative complications betweenMPHand fibrin glue.

Full Text

Functional improvement of focal cerebral ischemia injury by subdural transplantation of induced

pluripotent stem cells with fibrin glue.

Authors: Chen S.-J., Chang C.-M., Tsai S.-K., Chang Y.-L., Chou S.-J., Huang S.-S., Tai L.-K., Chen Y.-C., Ku H.-H., Li H.-Y., Chiou S.-H.

Publication Date: 2010

PMID: 359871830

Abstract

Ischemic stroke is the leading cause of disability in the world. Cell transplantation has emerged in various neurological diseases as a potential therapeutic approach in the postacute stroke phase. Recently, inducible pluripotent stem (iPS) cells showed potential for multilineage differentiation and provide a resource for stem cell-based therapies. However, whether iPS transplantation could improve the function of stroke-like model is still an open question. The aim of this study is to investigate the therapeutic effects of subdural transplantation of iPS mixed with fibrin glue (iPS-FG) on cerebral ischemic rats induced by middle cerebral artery occlusion (MCAO). We demonstrated an efficient method to differentiate iPS into astroglial-like and neuron-like cells which display functional electrophysiological properties. In vivo study firstly showed that the direct injection of iPS into damaged areas of rat cortex significantly decreased the infarct size and improved the motor function in rats with MCAO. Furthermore, we found that the subdural iPS-FG can also effectively reduce the total infarct volume and greatly improve the behavior of rats with MCAO to perform rotarod and grasping tasks. Importantly, analysis of cytokine expression in iPS-FG-treated ischemic brains revealed a significant reduction of pro-inflammatory cytokines and an increase of anti-inflammatory cytokines. Taken together, these results suggest that iPS cells could improve the motor function, reduce infarct size, attenuate inflammation cytokines, and mediate neuroprotection after ischemic stroke. Subdural iPS-FG could be considered as a more safe approach because this method can avoid iatrogenic injury to brain parenchyma and enhance recovering from stoke-induced impairment.

Full Text

The effects of fibrin glue on acute complete transection spinal cord injury. [Chinese]

Authors: Li Y., Zhao Q.

Publication Date: 2008

PMID: 550244616

Abstract

OBJECTIVE: To investigate the effects of fibrin glue on repair and regeneration of acute complete spinal cord injury. METHODS: Acute complete transaction spinal cord injury model were made in 10

adult healthy SD rats (female, weighing 250-300 g), randomized grouping: treated group (n=5) and control group (n=5). In the treated group, fibrin glue was implanted covering on the injury site and filling the lesion gap. In the control group, no treatment was given. At 4 weeks, the locomotor functions of the rats were detected by basso, beattie and bresnahan (BBB) score, then the means of immunohistochemistry were used to observe neurofilament(NF) and glial fibrillary acidic protein(GFAP). And image analysis was used to measure the quantify of the nerve fiber and the fibers area ratio of astrocyte. RESULTS: The BBB scores were 2.40 +/- 0.51 in control group, 3.00 +/- 0.45 in treated group, showing no significant difference (P > 0.05). By immunohistochemistry: a little positive NF cells and GFAP frame were found in control group; more positive NF cells and GFAP frame were found in treated group, the cells and frame grew toward the center but did not arrive at the center. Image analysis showed the amount of never fibers in treated group (rostral region: 113.10 +/- 20.75, caudal region: 73.60 +/- 33.61) was more than that in control group (rostral region: 45.50 +/- 17.18, caudal region 23.50 +/- 8.20), showing significant difference. The fibers area ratio of astrocyte in treated group (rostral region: 33.75% +/- 11.06%, caudal region: 27.75% +/- 7.15%) was more than that in control group(rostral region: 23.78% +/- 5.76%, caudal region: 19.78% +/- 5.17%), showing significant difference (P < 0.05). CONCLUSION: Fibrin glue can promote repair and regeneration of acute spinal cord injury.

Full Text

The long-term neurocompatibility of human fibrin sealant and equine collagen as biomatrices in experimental spinal cord injury.

Authors: Petter-Puchner A.H., Froetscher W., Krametter-Froetscher R., Lorinson D., Redl H., van Griensven M.

Publication Date: 2007

PMID: 44855539

Abstract

Introduction: While fibrin sealant (FS) and equine collagen (EC) have been used as scaffold materials in experimental spinal cord injury (SCI), questions concerning neurocompatibility still remain. In this study, we assessed potential adverse effects, as well as functional and histological impact of FS and EC in subtotal hemisection of the thoracic spinal cord (SC) in rats. Methods: 124 male rats were randomly assigned to four main groups (n = 31): Sham (SH), Lesion only (L), fibrin sealant (GFS) and equine collagen group (GEC). SH animals received laminectomy only; all other animals underwent subtotal lateral hemisection at T9. Treatment consisted of application of FS or EC into the lesion gap in GFS and GEC, which was left empty in L. GFS, GEC, L and SH were each further divided into 4 subgroups: One subgroup, consisting of 10 rats was subjected to behavioural and reflex testing before surgery and followed up on days 1,7, 14, 21, 28 post op and then sacrificed. Haemalaun or cresyl violet (CV) was used to identify neutrophils in parasagittal cord sections which were obtained on day 1 (n = 7). Sections stained for quantification of microglia/macrophages using ED-1 on day 3 (n = 7), day 7 (n = 7) and day 28 (n = 7 out of 10). Additionally, neural filament (NF) staining was chosen to detect axonal regeneration and the length of ingrowth into FS and EC, Luxol blue for myelination, Von Willebrand

factor for vascularisation, and glial fibrillary acidic protein (GFAP) staining for detection of astrocytes in glial scars on day 28. Results: No adverse effects were observed in the treatment groups. Compared to L, GFS and GEC performed significantly better in the Basso, Beattie, Bresnahan (BBB) score and hopping responses. Proprioceptive placing was markedly improved in FS and EC compared to L. Axonal regrowth was found in GFS and GEC - the regrowth in the GFS was accompanied by myelination and vascularisation. Glial scarring occurred in all groups. Discussion. Both biomatrices improved functional recovery compared to L and no adverse effects were perceived.

Full Text

Human amniotic membrane-derived mesenchymal stem cells combined with nerve growth factor and biologic fibrin glue transplantation in the treatment of bran injury in rats. [Chinese]

Authors: Wang H., Guan F.-X., Yang B., Qi Y.-J., Song L.-J., Du Y., Hu X., Hu W., Jiao H.-L., Li Y.

Publication Date: 2008

PMID: 354228909

Abstract

Background: Previous studies are on in vitro culture of mesenchymal stem cell differentiation. Few studies on mesenchymal stem cell differentiation in vivo or effects of cofactor on their differentiation. Objective: To study the amniotic membrane-derived mesenchymal stem cell (AD-MSC) transplantation on behavior, spatial learning and memory in traumatic brain injury rats, and the abilities to nerve growth factor (NGF), biologic fibrin glue (BFG) in AD-MSC transplantation. Design, Time and Setting: The cytology in vivo controlled study was performed at the Medical College of Zhengzhou University from July 2006 to January 2007. Materials: The placenta from healthy normal full-term fetus was obtained from Department of Gynaecology and Obstetrics, First Affiliated Hospital, Zhengzhou University. A total of 90 Wistar rats were equally and randomly assigned into a sham operation group, a model control group, a cell transplantation group, a cell + NGF group, a cell + BFG group. Methods: Fetal amniotic membrane was harvested from the placenta by blunt dissection under a sterile condition, made into monoplast suspension by trypsinization, and purified by adherece. At the third passage, AD-MSCs were used. Rats in the sham operation group underwent perforation. Rats in other groups were established into models of traumatic brain injury using free-failing epidural impact method. At 1 day following model induction, 40 mu L saline was infused into injury sites in the model control group. An equal volume of saline containing $1x10^7$ AD-MSCs were injected into rats in the cell transplantation group. Rats in the cell + NGF group were injected with $1x10^7$ AD-MSCs and 0.5 mu g NGF for successively for 2 weeks. Rats in the cell + BFG group were infused with AD-MSCs and 40 mu L BFG. Rats in the sham operation group did not receive cell transplantation. Main Outcome Measures: Ethology score; Latency was measured using Morris water maze test. Neuron specific enolase and glial fibrillary acidic protein expression was observed by immunohistochemistry. Results: At 7 days after transplantation, behavior score was significantly higher in the cell transplantation group, cell + NGF

group, cell + BFG group compared with the model control group. The increase was significantly lower in the cell transplantation group compared with the cell + NGF group and cell + BFG group (F=155.322, P < 0.05). At 3 weeks after the transplantation, the latency was significantly shorter in the cell transplantation group, cell + NGF group, cell + BFG group compared with the model control group. The shortened range was significantly smaller in the cell transplantation group compared with the cell + NGF group and cell + BFG group (F=22.678, P < 0.05). At 4 weeks following transplantation, AD-MSCs could differentiate into nerve cell in damage brain tissue, and express neural specific enolase and glial fibrillary acidic protein following combined transplantation of NGF and BFG (F=705.406, F=424.884, P < 0.05). Conclusion: AD-MSCs can improve behavior and spacial learning and memory abilities, express neural specific enolase and glial fibrillary acidic protein following differentiation. NGF and BFG may enhance efficacy of transplantation.

Full Text

Controlling bone morphogenetic protein diffusion and bone morphogenetic protein-stimulated bone growth using fibrin glue.

Authors: Patel V.V., Zhao L., Wong P., Kanim L., Bae H.W., Pradhan B.B., Delamarter R.B.

Publication Date: 2006

PMID: 43756293

Abstract

Study Design. An in vitro and in vivo study. Objective. To evaluate the ability of fibrin glue to limit diffusion of recombinant human bone morphogenetic protein (rhBMP)-2 and its ability to protect spinal nerves from rhBMP-2 stimulated bone growth. Summary of Background Data. Studies have shown bone morphogenetic protein (rhBMP-2) stimulated bone growth can encroach on the spinal canal and nerves, causing neural compression. More recently, rhBMP-2 use in the cervical spine has been associated with life-threatening swelling. Fibrin glue has been used as a biologic carrier but has not been evaluated for its ability to limit rhBMP-2. Methods. In phase 1 of the study, rhBMP-2 soaked absorbable collagen sponges (ACS) were encapsulated in fibrin glue and immediately incubated in physiologic lactated ringers solution at 38deg;C. Samples of solution were tested for rhBMP-2 concentration. In phase 2 of the study, rats were surgically treated with laminectomy and placement of rhBMP-2/ACS versus laminectomy and placement of fibrin glue before placement of rhBMP-2/ACS. After 8 weeks, animals were euthanized and imaged using micro-computerized tomography. Results. The diffusion study showed a significant limitation in rhBMP-2 diffusion when encapsulated in fibrin glue. The laminectomy study revealed blockage of bone formation by fibrin glue and protection of the spinal canal. Conclusions. Fibrin glue can limit the diffusion of rhBMP-2, and, thus, it can be used to help protect the spinal canal and nerve roots from rhBMP-2 stimulated bone growth. ©2006, Lippincott Williams & Wilkins, Inc.

Full Text

Topical application of fibrin adhesive in the rat brain: Effects on different cellular elements of the wound.

Authors: Muhammad A.K.M.G., Yoshimine T., Maruno M., Takemoto O., Hayakawa T.

Publication Date: 1997

PMID: 27143665

Abstract

Although fibrin adhesives are popular in the field of neurosurgery, the medical literature is devoid of study elucidating their effects on the brain tissue. To study the safety of applying fibrin glue to the brain and to explore new surgical potentialities, we implanted soft pellets made of fibrin glue into the brains of Wistar rat. Following 6 h and 3, 7 and 14 days post- implantation survival, the brains were removed and paraffin sections were processed for hematoxylin-eosin staining, as well as immunohistochemistry for microtubule-associated protein (MAP-1A) and glial fibrillary acidic protein. The changes in the neuronal and glial elements and also the numbers of inflammatory and endothelial cells in the vicinity of implanted fibrin glue pellets were compared with those of gelfilm pellets. The results demonstrated that topical application of fibrin glue to the brain causes significantly enhanced local accumulation of mononuclear cells and promoted angiogenesis close to the wound while not affecting the neuronal and glial elements. These findings suggest that fibrin glue can be considered as a safe supportive material for intradural procedures directly involving the brain tissue.

Full Text

A new surgical technique that allows proximodistal regeneration of 5-HT fibers after complete transection of the rat spinal cord.

Authors: Cheng H., Olson L.

Publication Date: 1995

PMID: 25368858

Abstract

Shortening of the spinal column has been regarded as one possible method to obtain cord-to-cord apposition after total transection of the spinal column. However, to further improve regenerative possibilities, the problems of inconstant bony fusion and cyst formations within the junctions must be resolved. Modifying the method of de Medinaceli on the rat thoracic spine, we attempted several fixation devices to achieve better interspinal fixation after spondylectomy and transection, including

transpedicular miniscrews, wiring of the transverse processes, and wiring of the posterior spinal processes. A dynamic model, based on retracting and compressing the cut ends of the spinal cord by means of adjustable fixation devices to allow swelling and shrinking of the stumps was also attempted to better compensate pathophysiologic changes of the transected cord. The best regeneration, as indicated by regrowth of 5-HT fibers below the level of transection, was obtained following application of fibrin glue and compressive wiring of posterior spinal processes. In this group, the distance between proximal and distal GFAP-rich spinal cord tissue (gap consisting of GFAP-poor components such as cysts, phagocytic cells, and scar tissue) of the two spinal cord stumps was also the shortest. With better approximation, the numbers of regenerated 5-HT fibers improved remarkably, suggesting that this descending fiber system is able to bridge the transection under these conditions.

Full Text

The effect of glial cell line-derived neurotrophic factor in fibrin glue on developing dopamine neurons.

Authors: Cheng H., Hoffer B., Stromberg I., Russell D., Olson L.

Publication Date: 1995

PMID: 25171793

Abstract

Glial cell line-derived neurotrophic factor (GDNF), a member of the transforming growth factor-beta superfamily, promotes the survival, morphological differentiation, and high-affinity dopamine (DA) uptake of cultured nigral DA neurons. In order to test potential methodology for peptide delivery in vivo, GDNF-containing fibrin glue balls (8 mug/ball) were incorporated with pieces of fetal ventral mesencephalon (E15) and transplanted into the anterior chambers of sympathetically denervated adult rats. Five weeks after grafting, the numbers of TH-positive neurons and the nerve fiber density were significantly higher in the ventral mesencephalic grafts treated with GDNF-containing glue balls than in those treated with vehicle. In addition, the laminin and GFAP immunoreactivities were similar between the two groups. These data support the concept that GDNF is a potent trophic factor for DA neurons in vivo and suggest that fibrin glue may provide a unique and safe means to permit prolonged delivery of trophic molecules to CNS tissues.

Full Text

Fibrin glue used as an adhesive agent in CNS tissues.

Authors: Cheng H., Almstrom S., Olson L.

Publication Date: 1994

PMID: 25239865

Abstract

One of the limitations of many bridging experiments in neural transplantation is that the CNS tissues cannot be sutured. Fibrin glue is a two-component system derived from whole blood which, when mixed, reproduces the final stage of blood coagulation and solidifies. Many experimental studies of humans and animals show that fibrin glue repair of peripheral nerves is almost equivalent to microsurgical sutures. In this study, we attempted to extend its use to CNS tissues and transplants. Two techniques were tried: (1) Bilateral parietal knife cuts were performed by stereotaxic technique in six rats. Fibrin glue was applied in the right-side cortical lesion. Immunohistochemistry using antisera to tyrosine hydroxylase (TH), glial fibrillary acidic protein (GFAP), laminin and neurofilament (NF) was essentially similar between the control and treatment groups. The immunoreactivity of each marker revealed no significant differences between the two groups on days 1, 7 and 30. There was no difference in terms of gliosis or microvascular proliferation. (2) Embryonic day 16 fetal locus coeruleus was grafted together with E16 cortex to the anterior chamber of sympathectomized eyes. In the six eyes of the glue treatment group, the parietal cortical piece and the locus coeruleus piece were joined together before grafting by immersing them in the solution of fibrin glue. In the eight eyes of the control group, pieces of parietal cortex and locus coeruleus were introduced individually and approximated by gently pressing the cornea. The sizes of double grafts showed no significant difference between groups during six weeks postgrafting. The immunohistochemical pictures using antisera against TH, GFAP and laminin were similar in both groups. Catecholaminergic fibers from the grafted locus coeruleus were found bridging over into the parietal cortical piece in both the control and treatment groups. There was no significant difference in TH-positive nerve fiber density between tissue glue-joined and control double intraocular grafts. In conclusion, fibrin glue can be used as an adhesive agent in CNS tissues without hampering the outgrowth of neurites or causing adverse tissue reactions in fetal or adult nervous tissues.

Full Text

Motor recovery and synaptic preservation after ventral root avulsion and repair with a fibrin sealant derived from snake venom.

Authors: Barbizan R, Castro MV, Rodrigues AC, Barraviera B, Ferreira RS, Oliveira AL

Publication Date: 2013

PMID: 23667596

Abstract

BACKGROUND: Ventral root avulsion is an experimental model of proximal axonal injury at the central/peripheral nervous system interface that results in paralysis and poor clinical outcome after

restorative surgery. Root reimplantation may decrease neuronal degeneration in such cases. We describe the use of a snake venom-derived fibrin sealant during surgical reconnection of avulsed roots at the spinal cord surface. The present work investigates the effects of this fibrin sealant on functional recovery, neuronal survival, synaptic plasticity, and glial reaction in the spinal motoneuron microenvironment after ventral root reimplantation. METHODOLOGY/PRINCIPAL FINDINGS: Female Lewis rats (7 weeks old) were subjected to VRA and root replantation. The animals were divided into two groups: 1) avulsion only and 2) replanted roots with fibrin sealant derived from snake venom. Post-surgical motor performance was evaluated using the CatWalk system twice a week for 12 weeks. The rats were sacrificed 12 weeks after surgery, and their lumbar intumescences were processed for motoneuron counting and immunohistochemistry (GFAP, Iba-1 and synaptophysin antisera). Array based qRT-PCR was used to evaluate gene regulation of several neurotrophic factors and receptors as well as inflammatory related molecules. The results indicated that the root reimplantation with fibrin sealant enhanced motor recovery, preserved the synaptic covering of the motoneurons and improved neuronal survival. The replanted group did not show significant changes in microglial response compared to VRA-only. However, the astroglial reaction was significantly reduced in this group. CONCLUSIONS/SIGNIFICANCE: In conclusion, the present data suggest that the repair of avulsed roots with snake venom fibrin glue at the exact point of detachment results in neuroprotection and preservation of the synaptic network at the microenvironment of the lesioned motoneurons. Also such procedure reduced the astroglial reaction and increased mRNA levels to neurotrophins and anti-inflammatory cytokines that may in turn, contribute to improving recovery of motor function.

Full Text

Corticospinal regeneration into lumbar grey matter correlates with locomotor recovery after complete spinal cord transection and repair with peripheral nerve grafts, fibroblast growth factor 1, fibrin glue, and spinal fusion.

Authors: Tsai EC, Krassioukov AV, Tator CH

Publication Date: 2005

PMID: 15804055

Abstract

Knowledge of which tracts are essential for the recovery of locomotor function in rats after repair is unknown. To assess the mechanism of recovery, we examined the correlation between functional recovery and axonal regeneration. All rats underwent complete cord transection and repair with peripheral nerves, fibroblast growth factor 1, fibrin glue, and spinal fixation. Repaired rats recovered both motor-evoked potentials recorded at the lumbar level and locomotor function. Cord retransection rostral to the repair abolished the recovery, indicating improvement was due to long tract regeneration. To determine which long tracts correlated with recovery, a novel technique of simultaneous bidirectional axonal tracing and immunohistochemical examination of axonal type was used to

quantitate the regeneration of corticospinal, rubrospinal, reticulospinal, vestibulospinal, raphespinal, propriospinal, serotonergic, and calcitonin gene-related peptide containing axons. Multiple linear regression analysis revealed recovery of function correlated only with regeneration of corticospinal axons into the gray matter of the lumbar spinal cord ($R = 0.977$, $p < 0.02$). For the first time, we show that regeneration of the corticospinal tract into the lumbar gray matter is a mechanism of functional locomotor recovery after complete cord transection and repair.

Full Text

Abrasion Plus Local Fibrin Sealant Instillation Produces Pleurodesis Similar to Pleurectomy in Rabbits.

Authors: Marchi E., de Carvalho M.V.H., Ventureli T.R., Fruchi A.J., Lazaro A., do Carmo D.C., Barreto T.Y.A.S., Dias B.V.B., Acencio M.M.P., Teixeira L.R., Light R.W.

Publication Date: 2016

PMID: 613227626

Abstract

Background Pleurodesis performed either by pleurectomy or pleural abrasion is recommended in the approach to primary spontaneous pneumothorax to avoid recurrence. However, the efficacy of parietal pleural abrasion in producing pleurodesis is questioned. This study aims to determine the efficacy of apical abrasion alone, abrasion plus fibrin sealant application, and pleurectomy in producing pleurodesis in rabbits. Methods Rabbits were subjected to video-assisted thoracic surgery alone (control) or to video-assisted thoracic surgery with apical gauze abrasion, abrasion plus fibrin sealant instillation, or apical pleurectomy. Blood samples were collected preoperatively and 48 h and 28 days postoperatively to measure total leukocytes (white blood cell count), neutrophil counts, and serum interleukin (IL)-8 levels. After 28 days the animals were sacrificed for macroscopic evaluation of the degree of apical pleurodesis and microscopic evaluation of local pleural fibrosis and collagen deposition. Results White blood cell and neutrophil counts were similar in all groups, whereas the serum IL-8 level peaked at 48 h in all groups and decreased after 28 days, except in the pleurectomy group. After 28 days the abrasion plus fibrin sealant and pleurectomy groups had significantly more pleural adhesions, pleural fibrosis, and collagen deposition than the abrasion alone group, mainly due to thick mature fibers. Conclusions Abrasion with local fibrin sealant instillation is as effective as pleurectomy in producing pleurodesis in rabbits. Apical pleurectomy elicits a more persistent elevation of serum IL-8 levels than apical abrasion alone or abrasion plus fibrin adhesive instillation.

Full Text

Enhanced Sealing by Hydrophobic Modification of Alaska Pollock-Derived Gelatin-Based Surgical Sealants for the Treatment of Pulmonary Air Leaks.

Authors: Mizuta R., Taguchi T.

Publication Date: 2017

PMID: 613648125

Abstract

Pulmonary air leaks are medical complications of thoracic surgery for which fibrin sealant is the main treatment. In this study, innovative sealants based on hydrophobically modified Alaska pollock-derived gelatin (hm-ApGltn) and a poly(ethylene)glycol-based 4-armed cross-linker (4S-PEG) have been developed and their burst strengths have been evaluated using fresh rat lung. The developed sealants show higher lung burst strength compared with the nonmodified original ApGltn (Org-ApGltn)-based sealant and a commercial fibrin sealant. The maximum burst strength of the hm-ApGltn-based sealant is 1.6-fold higher than the Org-ApGltn-based sealant ($n = 5$, $p < 0.05$), and 2.1-fold higher than the commercial fibrin sealant ($n = 5$, $p < 0.05$). Cell culture experiments show that modification of ApGltn with cholesteryl or stearoyl groups effectively enhances anchoring to the cell surface. In addition, binding constants between hm-ApGltn and extracellular matrix proteins such as fibronectin and fibrillin are increased. Therefore, the new hm-ApGltn/4S-PEG-based sealant has the potential for applications in thoracic surgery. (Figure presented.).

Full Text

Comparison of fibrin glue and vicryl sutures in conjunctival autografting for pterygium surgery.

Authors: Wang X., Zhang Y., Zhou L., Wei R., Dong L.

Publication Date: 2017

PMID: 616186217

Abstract

Purpose: To compare clinical parameters and the tear levels of inflammatory cytokines between pterygium surgery using sutures or fibrin glue. Methods: Fifty-six patients with primary pterygium were divided into the suture group and the glue group, in which the autograft was secured with 10-0 Vicryl sutures and fibrin glue, respectively. A questionnaire, slit-lamp examination, Schirmer test, and visual acuity test were performed in all participants. Real-time quantitative PCR (q-PCR) was used to analyze

the expression of genes in pterygium and healthy conjunctival tissues. Based on the qPCR results and literature reports, five inflammatory cytokines, including hepatocyte growth factor (HGF), fibroblast growth factor 2 (FGF2), transforming growth factor-beta1 (TGF-beta1), matrix metalloproteinase 2 (MMP2), and tumor necrosis factor-alpha (TNF-alpha), were selected, and their protein levels were measured with enzyme-linked immunosorbent assay (ELISA) in patient tears before surgery as well as at postoperative day 1, 7, and 30. Results: There are 28 patients in either the suture or the glue group. The average duration of surgery was 20.17 +/- 3.23 min for the glue group and 32.42 +/- 4.47 min for the suture group (p = 0.000). Visual acuity in both groups was improved (p = 0.002) after the surgical procedures. There were more symptoms in the suture group than in the glue group at postoperative day 7 (p = 0.002). Postoperative symptoms disappeared in both groups at 1 month after surgery. Recurrence was observed in one case in the glue group and in two cases in the suture group at the 6 month postoperative follow-up (p = 0.714). In comparison to the preoperative levels (4.33 +/- 0.43 ng/ml for the suture group; 4.20 +/- 0.26 ng/ml for the glue group), the levels of TNF-alpha in tears increased in the suture group (5.02 +/- 0.49 ng/ml, p = 0.016) and decreased in the glue group (3.84 +/- 0.35 ng/ml, p = 0.052) on postoperative day 1. The glue treatment induced higher HGF production (4.78 +/- 1.25 ng/ml) than the suture treatment (3.04 +/- 1.18 ng/ml) at postoperative day 1 (p = 0.020). Higher levels of TGF-beta1 in the glue group were detected at postoperative day 1 (3.71 +/- 0.18 ng/ml) and postoperative day 30 (4.50 +/- 0.51 ng/ml), compared to those in the suture group, respectively (2.74 +/- 0.21 ng/ml, p = 0.000 for day 1; 3.36 +/- 0.96 ng/ml, p = 0.017 for postoperative day 30).Conclusions: Fibrin glue is effective and safe for attaching conjunctival autografts with an easy surgical procedure, shortened operating time, and less postoperative discomfort. In the early postoperative period, the protein expression of inflammatory cytokines implicates that fibrin glue may induce accelerated healing and subdued inflammation on the ocular surface compared to sutures.

Full Text

Culture and characterization of oral mucosal epithelial cells on a fibrin gel for ocular surface reconstruction.

Authors: Sheth R., Neale M.H., Shortt A.J., Massie I., Vernon A.J., Daniels J.T.

Publication Date: 2015

PMID: 605676632

Abstract

Aim of the study: To develop a clinical grade fibrin gel for the culture of oral mucosal epithelial cells (OMEC) intended for ocular surface reconstruction in the treatment of limbal stem cell deficiency (LSCD).Materials and methods: Transparent fibrin gels composed of fibrinogen and thrombin were developed for the culture of epithelial cells. Oral mucosa was harvested from the buccal region of healthy volunteers and cultured as explants on fibrin gels. Tranexamic acid (TA), a clinically approved anti-fibrinolytic agent was added to prevent the fibrin gel from digesting due to cellular activity. The gels were stained for p63alpha (as a marker of poorly differentiated epithelial cells), CK19, CK13 and CK3 (expressed by OMEC). Epithelial cell stratification was observed using hematoxylin-eosin

staining.Results: Addition of TA prevented gels from dissolving during the culture period. OMEC proliferated on the fibrin gel and attained confluence over a 2-week period (+/-2 d) and exhibited a typical epithelial, cobblestone morphology. Basal OMEC exhibited positive staining for p63alpha while the superficial cells exhibited positive staining for CK3. The cells expressed a strong immunoreactivity for CK19 and CK13 suggesting that they retained a normal oral epithelial phenotype.Conclusion: Fibrin gels, maintained in the presence of TA, to control the rate of substrate degradation, provide a more robust yet transparent substrate for the culture and transplantation of cultured OMEC. The fibrin gels are easily standardized, the components commercially available, and produced from clinically approved materials. The resulting stratified OMEC-derived epithelium displays characteristics similar to that of a human cornea, e.g. CK3 expression. The conventional dependence on a murine feeder layer for support of epithelial cells is unnecessary with this technique and hence, provides for an attractive alternative for treatment of LSCD.

Full Text

Enhancement of posterolateral lumbar spine fusion using recombinant human bone morphogenetic protein-2 and mesenchymal stem cells delivered in fibrin glue.

Authors: Liu Z., Zhu Y., Zhu H., He X., Liu X.

Publication Date: 2016

PMID: 612804286

Abstract

Mesenchymal stem cells have shown great potential for accelerating bone healing. In the present study, we evaluate the efficacy of fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 composite for posterolateral spinal fusion in a rabbit model. Forty adult rabbits underwent posterolateral intertransverse fusion at the L5-L6 level. The animals were randomly divided into four groups based on the implant material: fibrin glue, fibrin glue/mesenchymal stem cells composite, fibrin glue-recombinant human bone morphogenetic protein-2 (fibrin glue/recombinant human bone morphogenetic protein-2) composite, and fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 composite. After six weeks, the rabbits were euthanized for manual palpation, radiographic examination, biomechanical testing, and histology. Manual palpation results showed that the fusion rate for fibrin glue, fibrin glue/mesenchymal stem cells, fibrin glue/recombinant human bone morphogenetic protein-2, and fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 was 0, 0, 40%, and 70%, respectively. Moreover, fusion rate determined by radiographic examination for fibrin glue, fibrin glue/mesenchymal stem cells, fibrin glue/recombinant human bone morphogenetic protein-2, and fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 was 0, 0, 40%, and 80%, respectively. Gray analysis showed that fibrin glue/recombinant human bone morphogenetic protein-2 group had higher ossification area and density than fibrin glue group; and fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 group had higher ossification area and density

than fibrin glue/recombinant human bone morphogenetic protein-2 group. Formation of continuous bone masses between L5 and L6 level in mesenchymal stem cells/recombinant human bone morphogenetic protein-2/fibrin glue group was further confirmed by computed tomography scanning and three-dimensional reconstruction. Biomechanical testing demonstrated that the fusion strength (flexion, extension, lateral bending, and axial rotation) in fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 group is significantly higher than that in fibrin glue/recombinant human bone morphogenetic protein-2 group. The formation of mature bone tissues between transverse processes of the fused specimens from both fibrin glue/recombinant human bone morphogenetic protein-2, and fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 groups was confirmed by HE staining, and quantitative real-time polymerase chain reaction results showed the upregulation of CD31, type I collagen, osteocalcin, and osteonectin in the fibrin glue/mesenchymal stem cells/recombinant human bone morphogenetic protein-2 group. In conclusion, our findings show that mesenchymal stem cells delivered with recombinant human bone morphogenetic protein-2 using fibrin glue as carrier are more effective in enhancing spine fusion than recombinant human bone morphogenetic protein-2 without mesenchymal stem cells in the rabbit model.

Full Text

Colonization of klebsiella pneumoniae inside fistula tracts a possible risk factor for failure of fibrin glue-assisted closure.

Authors: Wu X., Ren J., Wang G., Gu G., Li X., Ren H., Hong Z., Li J.

Publication Date: 2015

PMID: 52964262

Abstract

Goals: This study was designed to investigate the risk factors affecting glue-assisted closure (GAC) in the enterocutaneous fistula (ECF) patients receiving glue application. Background: ECF is a challenging problem in surgical practice, and it is difficult to resolve by spontaneous closure. Currently, GAC is popular when treating fistulas, but data related to risk factors are limited. Methods: We retrospectively analyzed 82 patients with 93 ECFs, who had autologous glue sealing from 2010 to 2012 in a referral center. Their demographic data, clinical records, and fistula characteristics were collected. Both univariate analysis and multivariate Cox proportional hazards model were used to determine the prognostic factors affecting closure. Results: During the 14-day treatment period, 78.5% (73/93) of the fistulas achieved GAC. We excluded 3 reopened fistulas and investigated 90 ECFs from 79 patients. Univariate analysis demonstrated that patients with high levels of CRP, high CRP: prealbumin ratio, elevated blood glucose, and specific pathogen colonization, together with lower GI location, greater output volume, and shorter tract length, had a poor outcome ($P<0.05$). Using multivariate analysis, monomicrobial and polymicrobial colonization with Klebsiella pneumoniae inside the fistula tracts (hazard ratio, 0.191; 95% confidence interval, 0.045-0.810; $P=0.025$) was a statistically significant risk factor for failure of fistula closure. Conclusions: The presence of monomicrobial and polymicrobial colonization with K. pneumoniae in fistulous tracts was an independent risk factor for failure of GAC in

patients receiving glue application. Better debridement of the tracts should be performed before the glue sealing.

Full Text

Treatment of hypertrophic scar in human with autologous transplantation of cultured keratinocytes and fibroblasts along with fibrin glue.

Authors: Taghiabadi E., Mohammadi P., Aghdami N., Falah N., Orouji Z., Nazari A., Shafieyan S.

Publication Date: 2015

PMID: 603669182

Abstract

Objective: Hypertrophic scar involves excessive amounts of collagen in dermal layer and may be painful. Nowadays, we can't be sure about effectiveness of procedure for hypertrophic scar management. The application of stem cells with natural scaffold has been the best option for treatment of burn wounds and skin defect, in recent decades. Fibrin glue (FG) was among the first of the natural biomaterials applied to enhance skin deformity in burn patients. This study aimed to identify an efficient, minimally invasive and economical transplantation procedure using novel FG from human cord blood for treatment of hypertrophic scar and regulation collagen synthesis. Materials and Methods: In this case series study, eight patients were selected with hypertrophic scar due to full-thickness burns. Human keratinocytes and fibroblasts derived from adult skin donors were isolated and cultured. They were tested for the expression of cytokeratin 14 and vimentin using immunocytochemistry. FG was prepared from pooled cord blood. Hypertrophic scars were extensively excised then grafted by simply placing the sheet of FG containing autologous fibroblast and keratinocytes. Histological analyses were performed using Hematoxylin and eosin (H&E;) and Masson's Trichrome (MT) staining of the biopsies after 8 weeks. Results: Cultured keratinocytes showed a high level of cytokeratin 14 expression and also fibroblasts showed a high level of vimentin. Histological analyses of skin biopsies after 8 weeks of transplantation revealed re-epithelialization with reduction of hypertrophic scars in 2 patients. Conclusion: These results suggest may be the use of FG from cord blood, which is not more efficient than previous biological transporters and increasing hypertrophic scar relapse, but could lead to decrease pain rate.

Full Text

Mesenchymal stem cells engrafted in a fibrin scaffold stimulate Schwann cell reactivity and axonal regeneration following sciatic nerve tubulization.

Authors: Cartarozzi L.P., Spejo A.B., Ferreira R.S., Barraviera B., Duek E., Carvalho J.L., Goes A.M., Oliveira A.L.R.

Publication Date: 2015

PMID: 601935431

Abstract

The present study investigated the effectiveness of mesenchymal stem cells (MSCs) associated with a fibrin scaffold (FS) for the peripheral regenerative process after nerve tubulization. Adult female Lewis rats received a unilateral sciatic nerve transection followed by repair with a polycaprolactone (PCL)-based tubular prosthesis. Sixty days after injury, the regenerated nerves were studied by immunohistochemistry. Anti-p75NTR immunostaining was used to investigate the reactivity of the MSCs. Basal labeling, which was upregulated during the regenerative process, was detected in uninjured nerves and was significantly greater in the MSC-treated group. The presence of GFP-positive MSCs was detected in the nerves, indicating the long term survival of such cells. Moreover, there was co-localization between MSCs and BNDF immunoreactivity, showing a possible mechanism by which MSCs improve the reactivity of SCs. Myelinated axon counting and morphometric analyses showed that MSC engrafting led to a higher degree of fiber compaction combined with a trend of increased myelin sheath thickness, when compared with other groups. The functional result of MSC engrafting was that the animals showed higher motor function recovery at the seventh and eighth week after lesion. The findings herein show that MSC. +. FS therapy improves the nerve regeneration process by positively modulating the reactivity of SCs.

Full Text

Endoscopic tissue shielding method with polyglycolic acid sheets and fibrin glue to cover wounds after colorectal endoscopic submucosal dissection (with video).

Authors: Tsuji Y., Ohata K., Gunji T., Shozushima M., Hamanaka J., Ohno A., Ito T., Yamamichi N., Fujishiro M., Matsuhashi N., Koike K.

Publication Date: 2014

PMID: 603253584

Abstract

Background Colorectal endoscopic submucosal dissection (ESD) has made it possible to resect large specimens in an en bloc fashion. However, this can lead to postoperative adverse events, such as perforation and bleeding. Prevention of adverse events after colorectal ESD is therefore an important goal. Objective To evaluate the utility of a shielding method using polyglycolic acid (PGA) sheets and

fibrin glue to manage ulcers after colorectal ESD. Design Prospective, single-arm, pilot study. Setting Single tertiary care center for colorectal ESD in Japan. Patients Ten patients with 10 colorectal tumors scheduled for ESD were enrolled between September and November 2012. Interventions Just after ESD, we placed PGA sheets on the mucosal defect with biopsy forceps. After the whole defect was covered, we sprayed fibrin glue through a special double-lumen spraying tube. We sprayed fibrinogen through 1 lumen and then thrombin through the other lumen. Main Outcome Measurements Success rate, mean procedure time, and adverse events associated with the covering technique and the persistence of PGA sheets at follow-up colonoscopy. Results All 10 tumors were successfully resected. Mean tumor size was 39.7 +/- 15.2 mm. All mucosal defects were successfully covered with PGA sheets. Mean procedure time was 18.7 +/- 15.9 minutes. No procedure-related adverse events occurred. Upon colonoscopy 9 to 12 days after ESD, the PGA sheets were still fixed on the whole defect in 8 patients. Limitations Small sample size. Conclusions Our technique, which uses PGA sheets and fibrin glue, appears to shield mucosal defects, and it may be effective in reducing postoperative adverse events.

Full Text

[' endoscopic submucosal dissection (ESD) is becoming the standard of care for colorectal tumors; however, troubleshooting for complications remains a challenge, particularly when dealing with large intraoperative perforations123. Here, we present a case where such a large perforation was successfully treated with polyglycolic acid (PGA) sheets and a purse-string suture method using a detachable snare.', ' 76-year-old woman was referred to our institution for treatment of a large flat-elevated rectal tumor. Colonoscopy revealed that the tumor involved two-thirds of the circumferential surface, and covered the area above and below the peritoneal reflection, and extended to the anal margin (.200a1). The entire lesion was soft, and magnifying chromoendoscopy using crystal violet staining identified type IV and V irregular low-pit patterns; thus, we diagnosed the lesion as adenoma or intramucosal adenocarcinoma. Computed tomography (CT) showed no lymph node or distant metastasis, and ESD was performed.', '2002Endoscopic findings of two-thirds of the circumferential flat-elevated type of rectal tumor. The tumor resembled a collection of small lesions, and the boundaries of some lesions were unclear.', ' lesion was difficult to dissect because of the high degree of fibrosis. However, when approximately 90200a% of the dissection was completed, a large, approximately 40200amm, perforation was identified (.200a2). The lesion was excised as quickly as possible, and the purse-string suture method was used to close the perforation (.200a3). PGA sheets were used to fill the gap, and fibrin glue was sprayed (20061). CT, obtained immediately after the procedure, showed fluid retention, increased lipid density around the rectum, and retroperitoneal emphysema extending around the right kidney. The patient was managed conservatively, She resumed eating 7 days post ESD and was discharged on Day 11.', '2002Giant perforation of the lower rectum, measuring 40200amm in size, located below the peritoneal reflection (areas marked with blue arrows). The serosa and retroperitoneal cavity were visible at the perforation site.', '2002Endoscopy images. detachable snare was spread around the perforation and fixed to the muscle layer or mucosa with clips. tightening the fixed detachable snare, the purse-string suture method was used to close the perforation. Polyglycolic acid sheets filled the gap, and fibrin glue was sprayed.', 'Video200612002Management of intraoperative giant perforation of colorectal endoscopic submucosal dissection.', ' colonoscopy performed 8 weeks after discharge showed mild postoperative stenosis, partial obstruction was not observed, and no local recurrence occurred (.200a4). The resected specimen was 80200a×200a66200amm in size and contained a 78200a×200a64200amm tumor. Histopathological analysis revealed high-grade tubular adenoma.', '2002Colonoscopy 8 weeks after endoscopic submucosal dissection showed mild stenosis but no passage obstruction.', 'Endoscopy_UCTN_Code_CPL_1AJ_2AD', 'Endoscopy E-Videos an open access online section, reporting on interesting cases and new techniques in gastroenterological endoscopy. All papers include a high quality video and all contributions are freely accessible online. Processing charges apply (currently EUR 375), discounts and wavers acc. to available. section has its own submission website

at://mc.manuscriptcentral.com/e-videos', ' would like to thank Editage (.editage.com) for English language editing.', 'Competing interests Mitsuhiro Fujishiro has received research grants from Olympus Corporation, Fujifilm Corporation, and HOYA Pentax Corporation, and honoraria from Olympus Corporation and Fujifilm Corporation. Yosuke Tsuji has received research grants from Olympus Corporation, GUNZE and HOYA Pentax Corporation. The remaining authors declare that they have no conflict of interest.']

The comparison of autoclaved autogenous bone and fibrin glue as BMP carriers for bone generation in a critical-size segmental defect in the Rat fibula.

Authors: Nam J.W., Kim H.J.

Publication Date: 2014

PMID: 71597326

Abstract

Bone morphogenic proteins (BMPs) have been shown to play an important role in bone formation during development and wound healing. Despite the good prospects for BMP applications, an ideal carrier system for BMPs has yet to be determined. The purpose of this study was to evaluate the possibility of an autoclaved autogenous bone(AAB) as a carrier for recombinant human BMP-2(rhBMP-2) and compare it to well known BMP carriers, AAB and fibrin glue (FG), in a rat fibula defect model. A critical size defect (6mm) of fibulawas created in each of 24 male Spraque-Dawley rats. They were placed in two groups, 6 rats each group, as follows. Group A: 6 rats with right resected and repositioned fibula segmental bones(autoclaved under 123C,0.2MPa, 10min.) with 10 rhBMP-2 on the (experimental) and without rhBMP-2 on left side (control). Group B: Prefabricated rhBMP-2/FG and FG blocks in size 1.5 x 1.5 x 6 mm were positioned on 12 fibula bony defect site (6 right bone defects: experimental, 6 left bone defects: control). The groupswere evaluated using histologic, radiologic, and Micro-CT methods following 2-, 4-, and 8-week healing intervals. Group A. Group B. Among the observed results for both A and B experimental groups we can highlight the following: I. In the gross and radiographic findings a complete union with ectopic bone was noticeable by the 2nd week and remodelation of the newly formed bone was observed in the 8th week. II. In the histomorphological and Micro-CT findings the formation from an immature to a mature bone was observed. From a low and irregular to normal bone morphology and density surrounded by a dense cortical bone and finally connecting to the pre-existing fibula. Among the two BMP carriers evaluated in this study, in terms of emission control and maintenance of the BMPs, the FG was more effective than AAB for bone regeneration. But, in terms of space maintenance the AAB showed a higher advantage over the FG. Therefore, we suggest the clinical applications of BMP carriers in a combination, FG-AAB, in order to use as much as possible the advantages offered by the BMP's osteoinductivity and these carriers' osteoconductivity and expect a faster wound healing, as well as functional, esthetic, and economic benefits.

Full Text

Prefabrication of vascularized grafts based on pre-differentiated adipose derived stem cells, fibrin sealant and porous calcium phosphate cement scaffold. [Chinese]

Authors: Yang P., Huang X., Wang C.-S., Wang K.-Z.

Publication Date: 2013

PMID: 373888290

Abstract

Background: Construction of vascularized bone substitutes to mimic free vascularized fibular grafting in treating large bone defects still remains challenges to researchers during the past years. Objective: To design and construct a new vascularized tissue-engineered bone graft using pre-differentiated adipose derived stem cells, fibrin sealant and porous calcium phosphate cement scaffold. Methods: Adipose derived stem cells isolated from rats were directly differentiated to endothelial cells and then incorporated in fibrin sealant and porous calcium phosphate cement scaffolds in vitro. Subsequently, the different composites of the three groups including vascularized tissue-engineered bone scaffold (group A), fibrin sealant and porous calcium phosphate cement scaffold (group B) and porous calcium phosphate cement scaffold (group C) were directly embedded into the quadriceps of the rats. Histological quantitative analysis and western blot assay were conducted 2 and 4 weeks after implantation. Results and Conclusion: The pre-differentiated adipose derived stem cells were demonstrated in good condition after 7 days co-culturing with the fibrin sealant and porous calcium phosphate cement scaffold. The results of in vivo experiments showed that the scaffolds were in-grown together with fibrous connective tissues and blood vessels. Newly formed vessels and immature capillaries were observed in the group A. The vessel density, vessel diameter and vascular endothelial growth factor C expression in the group A were significantly higher than those in the groups B and C. Our findings demonstrated that compared with simply fibrin sealant and porous calcium phosphate cement scaffold, the combination of pre-differentiated adipose derived stem cells (endothelial differentiation) and fibrin sealant can achieve rapid angiogenesis of porous calcium phosphate cement scaffold.

Full Text

Bio-oss combined with fibrin glue and bone morphogenetic protein-2 to repair mandibular defects. [Chinese]

Authors: Tian G., Xu X.-G., Zhou Z.-H., Gao J.-Y.

Publication Date: 2013

PMID: 373924181

Abstract

Background: Bio-oss granular structure is normally used for hole-shaped defects in the form of filling transplantation, but it is difficult to forming for more than three-wall defects. Objective: To evaluate the osteogenic activities of Bio-oss after combination with fibrin glue and bone morphogenetic protein-2 in the repair of canine mandibular defects. Methods: The second and fourth premolar teeth and the second molar teeth were extracted bilaterally in nine hybrid canines, resulting in 1 cm x 1 cm bone defect. Bio-oss, Bio-oss+fibrin glue and Bio-oss+fibrin glue+bone morphogenetic protein-2 were implanted into bone defects of the second, fourth premolar teeth and the second molar teeth, respectively.Results and Conclusion: Stage I healing of soft tissues was achieved in all animals. Bio-oss was closely combined with fibrin glue, which was difficult to be separated. The proportion of new bone was higher in the Bio-oss+fibrin glue+bone morphogenetic protein-2 group than in the other two groups at 4, 8, and 12 weeks after extraction ($P < 0.05$). It shows that fibrin glue can solve the difficulty in Bio-oss formation, and Bio-oss combined with bone morphogenetic protein-2 can promote osteogenic activities.

Full Text

L-PRP/L-PRF in esthetic plastic surgery, regenerative medicine of the skin and chronic wounds.

Authors: Cieslik-Bieleck A., Choukroun J., Odin G., Dohan Ehrenfest D.M.

Publication Date: 2012

PMID: 364831853

Abstract

The use of platelet concentrates for topical use is of particular interest for the promotion of skin wound healing. Fibrin-based surgical adjuvants are indeed widely used in plastic surgery since many years in order to improve scar healing and wound closure. However, the addition of platelets and their associated growth factors opened a new range of possibilities, particularly for the treatment of chronic skin ulcers and other applications of regenerative medicine on the covering tissues. In the 4 families of platelet concentrates available, 2 families were particularly used and tested in this clinical field: L-PRP (Leukocyte- and Platelet-rich Plasma) and L-PRF (Leukocyte- and Platelet-Rich Fibrin). These 2 families have in common the presence of significant concentrations of leukocytes, and these cells are important in the local cleaning and immune regulation of the wound healing process. The main difference between them is the fibrin architecture, and this parameter considerably influences the healing potential and the therapeutical protocol associated to each platelet concentrate technology. In this article, we describe the historical evolutions of these techniques from the fibrin glues to the current L-PRP and L-PRF, and discuss the important functions of the platelet growth factors, the leukocyte content and the fibrin architecture in order to optimize the numerous potential applications of these products in regenerative medicine of the skin. Many outstanding perspectives are appearing in this field

and require further research.

Full Text

Effect of polyglycolic acid sheets with fibrin glue (MCFP technique) on the healing of wounds after partial resection of the border of the tongue in rabbits: A preliminary study.

Authors: Yonezawa H., Yamada S.-I., Yanamoto S., Yoshitomi I., Kawasaki G., Umeda M.

Publication Date: 2012

PMID: 51558041

Abstract

The aim of this study was to examine the effectiveness of covering wounds to the tongue with a polyglycolic acid (PGA) sheet and fibrin glue. Eighteen mature male Japanese white rabbits had a unilateral glossectomy involving an area 10 mm x 10 mm x 2 mm. After glossectomy the tongues were covered with PGA sheets 8 mm x 8 mm in size and fibrin glue (mucosal defect covered with fibrin glue and polyglycolic acid sheet = MCFP) 1 week after the operation (n = 3), after 2 weeks (n = 3), and after 4 weeks (n = 3). In control groups, after 1, 2, and 4 weeks (n = 3 in each group), the partially resected tongues were closed with absorbable sutures (polyglactin 910). One week (experimental and control groups 1), 2 weeks (experimental and control groups 2) and 4 weeks (experimental and control groups 3) after operation the tongues were harvested and stained for microscopic examination. Histological examination showed that the covered wound surface had not epithelialised and the basal layer had yet to form in experimental group 1, but had formed in experimental group 2. However, in control group 1, epithelialisation of the sutured wound had begun. Immunohistochemical examination showed that, in experimental group 1, the non-uniform epithelial layer of the covered wound surface expressed cytokeratin AE1/AE3, and the epithelial and connective tissue layers stained strongly for FGF-2. Similar results were obtained in experimental group 2, whereas in experimental group 3, FGF-2 was expressed only in the connective tissue layer, and epithelialisation was complete. However, in control group 1, AE1/AE3 was expressed in the epithelial layer, and FGF was expressed in the connective tissue layer beneath the basal layer. In control groups 2 and 3, AE1/AE3 and FGF-2 were expressed in patterns similar to those in experimental groups 2 and 3. We suggest that this method is useful and the operation is simple. However, further testing of the method is needed and it should be widely used clinically before it is recommended. © 2011 The British Association of Oral and Maxillofacial Surgeons.

Full Text

Injectable calcium phosphate cement and fibrin sealant recombined human bone morphogenetic

protein-2 composite in vertebroplasty: An animal study.

Authors: Qian G., Dong Y., Yang W., Wang M.

Publication Date: 2012

PMID: 368010781

Abstract

Polymethylmethacrylate (PMMA) is currently the most commonly-used material, but it may induce adjacent vertebral fracture due to low degradation and high strength. Our study evaluated the feasibility of injectable calcium phosphate cement (ICPC) and fibrin sealant (FS) as an injectable compound carrier of human bone morphogenetic protein-2 (rhBMP-2) in New Zealand rabbits for vertebroplasty. Results showed ICPC/FS/rhBMP-2 composites induced alkaline phosphatase most effectively at 2 and 4 weeks after implantation. Histological examination confirmed that new bone and vessels developed at 4 weeks in the ICPC/FS/rhBMP-2 group. At 2 weeks, parts of the ICPC/FS/rhBMP-2 cement degraded with mature bone tissues and neovascularization. New bone was observed by MicroCT to form early and massively, and the ossification was almost synchronous with the material degradation. In the PMMA Group, however, no new bone formation or material degradation was found. The stiffness and tension of vertebral bodies implanted with ICPC/FS/rhBMP-2 were weaker than those of normal vertebral bodies as well as vertebral bodies implanted with PMMA at 4 weeks ($p<0.05$). At 2 weeks, the stiffness and tension of vertebral bodies implanted with ICPC/FS/rhBMP-2 became strong; no significant difference was noted in the stiffness and tension, compared with normal vertebral bodies ($p>0.05$), while they were significantly lower, compared with vertebral bodies implanted with PMMA ($p<0.05$). It is concluded that, with good characteristics of osteoinductivity, the bone substitution is synchronous with material degradation.

Full Text

Application of fibrin glue in conjunctival autograft surgery in rabbit pterygia model. [Chinese]

Authors: Cao L., Song Y., Wu Y., Sun Z.-M., Huang L.-L., Yu J.-F.

Publication Date: 2012

PMID: 364934826

Abstract

Background: Pterygia is a clinical common disease. A lot of surgical methods are developed to decrease the recurrence rate. Resent years, the application of fibrin glue is receiving more and more attention. Objective: This study was to explore the effects of fibrin glue in decreasing inflammatory

irritation and its mechanism. Methods: Pterygia models were created in 12 clean rabbits by exsection of limbal tissue and topical administration of 1.25% diluted hydrochloric acid, and then the conjunctival autograft surgery was performed in the experimental rabbits.The conjunctival flap was sutured in the left eyes, and the conjunctival wound was closed using fibrin glue in the right eyes. The operation duration for each group was documented and compared. The irritation sign was examined under the slit lamp in all the rabbits 1 week and 4 weeks respectively. The expressions of vascular endothelial growth factor (VFGF) and basic fibroblast growth factor (bFGF) proteins in the conjunctiva tissue were detected by immunochemistry, and the expressions of VFGF mRNA and bFGF mRNA in the conjunctival tissue were determined by reverse transcription polymerase chain reaction (RT-PCR). Results: The operative duration was (21.3+/-0.2) minutes in suture group and (10.1+/-0.1) minutes in the fibrin glue group with a significant difference between two groups ($t=102.242$, $P<0.05$). From 1 week through 4 weeks, the hyperemiain degree was obviously slight in fibrin glue group compared with suture group. Immunochemistry showed that VEGF and bFGF proteins were expressed mainly in the cytoplasm of conjunctival epithelium layer. The positive response intensity was weaker in the fibrin glue group than in suture group 1 week and 4 weeks after operation. RT-PCR revealed that the expression level of VEGF mRNA was significantly lower in fibrin glue group than in suture group, and the VEGF mRNA was gradually decreased with the time lapse ($Fgroup=174.443$, $P=0.000$; $Ftime=231.459$, $P=0.000$).The similar outcomes were found in the expression of bFGF mRNA ($Fgroup=41.727$, $P=0.000$; $Ftime=55.417$, $P=0.000$). Conclusions: The use of fibrin glue can shorten the operation duration and reduce postoperation inflammatory reaction. The downregulation of VEGF and bFGF in tissue is the possible mechanism of remitting irritation sign, which allows a reduce of the recurrence rate of pterygia.

Full Text

A new type of bone stuff with bone morphogenetic protein is used in vertebroplasty.

Authors: Qian G., Yang W.-C., Wang M.-H., Dong Y.-H.

Publication Date: 2012

PMID: 365784308

Abstract

BACKGROUND: Calcium phosphate bone cement (CPC) has good biocompatibility and no disadvantages of polymethyl methacrylate (PMMA). CPC with recombinant human bone morphogenetic protein-2 (rhBMP-2) has a microporous structure, and its clinical value can be improved in percutaneous vertebroplasty. OBJECTIVE: To evaluate the feasibility of injectable CPC and fibrin sealant (FS) combined with rhBMP-2 in vertebroplasty of New Zealand white rabbits to replace PMMA. METHODS: CPC/FS/rhBMP-2 was prepared. Tight muscle pouch model in mice was used to evaluate the osteoinductive activities of the implant materials. Imitation of vertebral plasty was used to observe the biomechanical changes of new composite material and PMMA after their implantation. RESULTS AND CONCLUSION: At 2 and 4 weeks of CPC/FS/rhBMP-2 implantation, alkaline phosphatase levels were the highest. At 4 weeks of CPC/FS/rhBMP-2 implantation, new bone formation and chondrocyte maturation could be seen, and the compressive strength and torsion strength were obviously lower than those of the normal vertebral and PMMA implantation ($P < 0.05$). After 8 weeks of implantation,

part of the CPC/FS/rhBMP-2 cement was degraded with some increases in compressive strength and torsion strength, and the torsion strength was similar with that of the normal vertebral, but was lower than that of PMMA implantation ($P < 0.05$). Micro CT showed that the new bone was plenty and its formation was in the early stage, and there was no material absorption or surrounding bone ingrowth could be seen in PMMA. It is indicated that good bone induction and bone conduction can be obtained after CPC/FS/rhBMP-2 implantation, and the degradation of CPC/FS/rhBMP-2 can synchronize with new bone formation to achieve normal bone healing. CPC/FS/rhBMP-2 is expected to replace PMMA in vertebral plasty.

Full Text

Effect of intraoperative platelet-rich plasma and fibrin glue application on skin flap survival.

Authors: Findikcioglu F., Findikcioglu K., Yavuzer R., Lortlar N., Atabay K.

Publication Date: 2012

PMID: 365905444

Abstract

The experiment was designed to compare the effect of intraoperative platelet-rich plasma (PRP) and fibrin glue application on skin flap survival. In this study, bilateral epigastric flaps were elevated in 24 rats. The right-side flaps were used as the control of the left-side flaps. Platelet-rich plasma, fibrin glue, and thrombin had been applied under the flap sites in groups 1, 2, and 3, respectively. Five days later, all flap pedicles were ligated. Necrotic area measurements, microangiography, and histologic and immunohistochemical evaluations were performed to compare the groups. Platelet-rich plasma reduced necrotic area percentages as compared with other groups. Histologically and microangiographically increased number of arterioles were observed in PRP groups. Thrombin when used alone increased flap necrosis. Vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor A3 primary antibody staining showed increased neovascularization and reepithelialization in all PRP-applied flaps. This study demonstrated that PRP, when applied intraoperatively under the skin flap, may enhance flap survival. Thrombin used alone was found to be unsuitable in flap surgery.

Full Text

Comparative in vivo study of injectable biomaterials combined with BMP for enhancing tendon graft osteointegration for anterior cruciate ligament reconstruction.

Authors: Pan W., Wei Y., Zhou L., Li D.

Publication Date: 2011

PMID: 361752462

Abstract

This study was to compare effect of osteointegration of grafted tendon in bone tunnels between injected calcium phosphate cement (ICPC) and injected fibrin sealant (IFS) combined with bone morphogenetic protein (BMP) after anterior cruciate ligament (ACL) reconstruction. ACL reconstruction was performed bilaterally in 51 rabbits. ICPC-BMP composite was injected into one knee, with the contralateral knee IFS-BMP composite. The rabbits were killed at postoperative weeks 2, 6, and 12 for testing. Histological observations showed the ICPC composite gradually increased the new bone formation during the whole healing process, while the IFS composite had a burst effect on enhancing the healing of tendon-to-bone at 2 and 6 weeks. By 12 weeks, there was more new cartilage and new bone in the interface in the ICPC-bBMP group. Micro-CT showed that the values of BMD in the ICPC-bBMP group were lower than those in the IFS-bBMP group at 6 weeks, while the values in the ICPC-bBMP group were higher than those in the IFS-bBMP group at 12 weeks ($p > 0.05$). Fluorescent labels showed that the rate of new bone formation of IFS-BMP composite was significantly higher than that of ICPC composite at 6 weeks (3.45+/-0.62 mum/day vs. 2.93+/-0.51 mum/day), but the rate was decreased compared with ICPC composite at 12 weeks (2.58+/-0.72 mum/day vs. 3.05+/-0.68 mum/day; $p < 0.05$). Biomechanically, the ultimate failure load in the ICPC-BMP group was always higher than that in the IFS-BMP group. It is evident that the ICPC composite achieved a more prolonged osteogenic effect than that by IFS composite.

Full Text

Effect of fibrin glue associated with antisense to PCNA on preventing restenosis of vein grafts.

Authors: Wan L., Wang W.-j., Cao Y.-p., Wang Q., Liu J.-c.

Publication Date: 2011

PMID: 365397404

Abstract

BACKGROUND: Preliminary findings show that fibrin glue is not only a good non-restrictive, extravascular biodegradable stent, but also can prevent intimal and medial hyperplasia of vein grafts. It is also a good drug delivery system that can improve the extravascular membrane gene transfection efficiency. OBJECTIVE: To verify the effect of fibrin glue associated with antisense to PCNA on preventing restenosis of vein grafts. METHODS: Rabbit models of external jugular vein carotid artery bypass grafting were prepared and then randomized into model group, fibrin glue group and fibrin glue+antisense group. Commercially available fibrin glue and fibrin glue mixed with adenovirus

expressing the antisense oligocleotides to PCNA were applied separately around vein grafts in the latter two groups, respectively. RESULTS AND CONCLUSION: Twenty-eight days after operation, the intimal and medial thickness and area was increased obviously in the model group and decreased significantly in the fibrin glue group (P < 0. 01). A significant difference in the intimal and medial thickness and area was found between the fibrin glue group and fibrin glue+antisense group (P < 0. 05). The mRNA and protein expressions of PCNA in the fibrin glue+antisense group was lower than those in the fibrin glue group (P < 0. 05). The expression of PCNA in vein grafts can be inhibited by adventitial delivery of antisense to PCNA. The fibrin glue mixed with antisense has a synergistic effect on reducing the intimal and medial thickness and area of vein grafts.

Full Text

Transplantation of muscle-derived stem cells plus biodegradable fibrin glue restores the urethral sphincter in a pudendal nerve-transected rat model.

Authors: Xu Y., Song Y.F., Lin Z.X.

Publication Date: 2010

PMID: 360044640

Abstract

We investigated whether fibrin glue (FG) could promote urethral sphincter restoration in muscle-derived stem cell (MDSC)-based injection therapies in a pudendal nerve-transected (PNT) rat, which was used as a stress urinary incontinence (SUI) model. MDSCs were purified from the gastrocnemius muscles of 4-week-old inbred female SPF Wistar rats and labeled with green fluorescent protein. Animals were divided into five groups (N = 15): Sham (S), PNT (D), PNT+FG injection (F), PNT+MDSC injection (M), and PNT+MDSC+FG injection (FM). Each group was subdivided into 1- and 4-week groups. One and 4 weeks after injection into the proximal urethra, leak point pressure (LPP) was measured to assess urethral resistance function. Histology and immunohistochemistry were performed 4 weeks after injection. LPP was increased significantly in FM and M animals after implantation compared to group D (P < 0.01), but was not different from group S. LPP was slightly higher in the FM group than in the M group but there was no significant difference between them at different times. Histological and immunohistochemical examination demonstrated increased numbers of surviving MDSCs (109 +/- 19 vs 82 +/- 11/hpf, P = 0.026), increased muscle/ collagen ratio (0.40 +/- 0.02 vs 0.34 +/- 0.02, P = 0.044), as well as increased microvessel density (16.9 +/- 0.6 vs 14.1 +/- 0.4/hpf, P = 0.001) at the injection sites in FM compared to M animals. Fibrin glue may potentially improve the action of transplanted MDSCs to restore the histology and function of the urethral sphincter in a SUI rat model. Injection of MDSCs with fibrin glue may provide a novel cellular therapy method for SUI.

Full Text

Effect of recombinant human bone morphogenetic protein-2/fibrin sealant implatation combined with core decompression on treating avascular necrosis of the femoral head in a rabbit. [Chinese]

Authors: Sun M.-L., Xu H., Wang J.-G.

Publication Date: 2009

PMID: 354529195

Abstract

Background: Bone morphogenetic protein-2 has been previously proved to not only stimulate and different bone tissue-derived cells, but also induce differentiation from cell strain into osteoblasts; however, direct application of bone morphogenetic protein has poor effects on repairing bone defects. Objective: To study new bone formation in a rabbit model of avascular necrosis of the femoral head (ANFH) following recombinant human bone morphogenetic protein-2 (rhBMP-2)/fibrin sealant (FS) implantation combining with core decompression. Design, Time and Setting: A randomized controlled animal experiment was performed at the Affiliated Hospital of Medical College of Chinese People's Armed Police Force from January 2005 to December 2007. Materials: Composite was made by rhBMP,2 and FS, and the final concentration of rhBMP-2 was 1 mg/L. Methods: Animal models of ANFH were made by injecting hormone. The rabbits were randomly divided into three groups, including rhBMP-2/FS implantation group, rhBMP-2 implantation group, and core decompression alone group. Main Outcome Measures: Signal changes of femoral head and sclerotin were detected using MRI method; new bone formation was observed under optic microscopy; calcium content was measured using atomic absorrtion spectrophotometer. Results: MRI indicated that new bone replaced primary bone defect channel at week 8 after rhBMP-2/FS implantation. A few of new bones were observed in the rhBMP-2 implantation group, and fiber tissue was still observed in the core decompression alone group. Morphology suggested that a great quantity of mature bone trabecula and plate-shaped bone replaced primary bone defect channel at week 8 after rhBMP-2/FS implantation. Bone defect was decreased in the rhBMP-2 implantation group, accompanying with a few of bone trabecula and blood capillary but a large quantity of fiber tissues. At week 8 after core decompression alone, bone defect was decreased, and a few of new bones were observed. Fiber tissue still existed in the center, and any bone tissue did not fill in it. Calcium content in the rhBMP-2/FS implantation group was greater than rhBMP-2 implantation group and core decompression alone group ($P < 0.01$). Conclusion: Bone morphogenetic protein can induce new bone formation in ischemic and necrotic femoral head; in addition, the rhBMP-2/FS composite can significantly induce and improve new bone formation.

Full Text

Applications of platelet-rich fibrin matrix in facial plastic surgery.

Authors: Sclafani A.P.

Publication Date: 2009

PMID: 355703016

Abstract

Platelet concentrates enjoyed some clinical popularity in facial plastic surgery several years ago. However, interest waned due to expense, amount of blood required, equipment, space, and staff needed, and lack of clinically significant benefit. A novel, simple method of preparing an autologous platelet derivative (Selphyl; Aesthetic Factors, Princeton, NJ) allows rapid and inexpensive generation of a platelet-rich fibrin matrix (PRFM) that can be used to enhance healing after facial procedures as well as to rejuvenate the face without tissue manipulation. PRFM provides autologous, natural, but concentrated platelet growth factor release and stimulation of surrounding tissue. This article describes its use for cosmetic facial applications. Copyright @copy; 2009 by Thieme Medical Publishers, Inc.

Full Text

Staged-injection procedure to prevent cement leakage during vertebroplasty: An in vitro study.

Authors: Wu Z.-X., Wei L., Hu Y.-Y., Wang H.-Q., Wan S.-Y., Wang J., Han Y.

Publication Date: 2007

PMID: 350303689

Abstract

STUDY DESIGN. Fibrin sealant (FS) combined with or without growth factor was used to improve the micro-architectural and biomechanical properties of vertebral body in osteoporotic ovine spine. OBJECTIVE. To analyze the treatment effects of bovine bone morphogenetic protein (bBMP) combined with FS on osteopenic ovine vertebral architecture, bone mineral density, and biomechanics in vivo. SUMMARY OF BACKGROUND DATA. Vertebroplasty and kyphoplasty were used to treat spinal osteoporosis. They can increase strength of vertebrae physically. However, each has specific disadvantages. bBMP could rapidly increasing bone formation and suppressing bone resorption, but little is known about its effect on ovariectomized-induced osteoporosis. METHODS. Six sheep underwent ovariectomy and were placed on a low-calcium diet. Twelve months later, according to Ladin square design, L4-L6 vertebrae in all sheep were randomly assigned to 3 treatment groups: A (30 mg bBMP/1.5 mL FS), B (30 mg bBMP) and C (1.5 mL FS). All materials were injected into the assigned vertebra transpedicularly. Animals were killed 3 months after injection, and bone mineral density (BMD), biomechanics, and histomorphometry were assessed. Analysis of variance was used to determine effects of bBMP/FS (alpha = 0.05). RESULTS. The BMD in Group 1 was 17.1% and 14.7% higher than that in Group 2 and Group 3, respectively. The micro-CT reconstruction analysis showed that the density and connectivity of trabecular bone in bBMP/FS treated vertebrae were higher than those in control groups. The mechanical properties (yield stress, ultimate stress, energy absorption,

bone modulus) of the vertebrae were also significantly higher. In this study, local bBMP/FS treatment showed a positive trend in improving BMD, histomorphometric parameters, and mechanical strength of osteoporotic vertebra. Slow release of bBMP using FS appeared to be an effective method of protein delivery. CONCLUSION. The use of bBMP/FS in the treatment of vertebral osteoporosis in an attempt to enhance bone strength merits further study.

Full Text

A comparative histologic analysis of tissue-engineered bone using platelet-rich plasma and platelet-enriched fibrin glue.

Authors: Zhu S.-J., Choi B.-H., Jung J.-H., Lee S.-H., Huh J.-Y., You T.-M., Lee H.-J., Li J.

Publication Date: 2006

PMID: 44094158

Abstract

Objective: The aim of this study was to compare the effects of platelet-rich plasma (PRP) and platelet-enriched fibrin glue on bone formation in bone tissue engineering. Study design: PRP was mixed with bone marrow mesenchymal stem cells and bone morphogenetic protein-2 (BMP-2), and the composites were injected into the subcutaneous space on the dorsum of nude mice. On the contralateral side of the dorsum, platelet-enriched fibrin glue/bone marrow mesenchymal stem cells/BMP-2 composites were injected. Bone formation was evaluated after 12 weeks. Results: The volumes of subcutaneous nodules formed in nude mice were 55 +/- 18 muL at the PRP/bone marrow mesenchymal stem cells/BMP-2 sites and 135 +/- 27 muL at the platelet-enriched fibrin glue/bone marrow mesenchymal stem cells/BMP-2 sites. Histomorphometric analysis demonstrated that the nodules contained 14.9 +/- 4.1% newly formed bone when using PRP and 19.8 +/- 3.6% newly formed bone when using platelet-enriched fibrin glue. Conclusion: The results indicated that the osteogenic characteristics of platelet-enriched fibrin glue are superior to PRP in bone tissue engineering.

Full Text

Sutureless amniotic membrane fixation using fibrin glue for ocular surface reconstruction in a rabbit model.

Authors: Szurman P., Warga M., Grisanti S., Roters S., Rohrbach J.M., Aisenbrey S., Kaczmarek R.T., Bartz-Schmidt K.U.

Publication Date: 2006

PMID: 44620133

Abstract

PURPOSE: Amniotic membrane transplantation has become an important treatment option for corneal surface reconstruction. However, suture fixation of the transplant has various disadvantages like corneal irritation, scarring, graft loss due to membrane shrinkage, and the need for subsequent suture removal. Replacement of sutures by bioadhesives might be an advantageous alternative. This controlled study was designed to evaluate a new sutureless technique for amniotic membrane fixation onto the corneal surface by using fibrin glue. METHODS: Standardized disks of cryopreserved amniotic membranes were transplanted onto the deepithelialized cornea of 12 rabbits using either conventional suture fixation or a new fibrin glue technique. The rabbits were followed-up with slit-lamp examination and fluorescein staining until epithelialization was completed. Consecutively, the rabbits were killed and the eyes processed for histology and immunohistochemistry for cytokeratin-3. RESULTS: All membranes of both groups stayed in place throughout the follow-up time and showed a progressive graft epithelialization that was completed after 12 days. Whereas suture-fixated membranes showed progressive tissue shrinkage, fibrin-glued sheets remained unaltered. In the bioadhesive group, histology revealed a smooth fibrin layer in the graft-host interface and a continuous, stratified layer of cytokeratin-3 expressing corneal epithelial cells on the membrane surface. In contrast, suture-fixated membranes showed contracted and prominent membrane edges with epithelial ingrowth into the submembrane interface. CONCLUSION: Our results demonstrate the general feasibility of reproducible and reliable sutureless amniotic membrane fixation onto the corneal surface in rabbits. Stable adherence is maintained until epithelialization is completed. The sutureless technique gives sufficient manipulation time for the sheet before the final cross-linking process is completed. Furthermore, several advantageous characteristics could be demonstrated as increased biocompatibility, better epithelialization pattern and the lack of membrane shrinkage. © 2006 Lippincott Williams & Wilkins, Inc.

Full Text

Multicellular growth factor in the repair of articular cartilage defects with chondrocyte-improved fibrin glue bracket. [Chinese]

Authors: Zhu L.-X., Jin A.-M., Li Q., Lin L.-J., Chi D.-Z., Min S.-X.

Publication Date: 2006

PMID: 46128172

Abstract

Aim: To study the effect of improved fibrin glue bracket, chondrocyte module, constructed by multicellular growth factors such as fibroblast growth factor (FGF) beta, transforming growth factor (TGF) beta1 and bone induction morphogenetic protein-6 in repairing the defection of articular

cartilage. Methods: The experiment was conducted in the Central Laboratory and Department of Orthopedics of Zhujiang Hospital Affiliated to Southern Medical University between December 2004 and June 2005. Forty-nine healthy New Zealand rabbits were selected, including one rabbit of 3 weeks old and 48 rabbits of 3 months old. Autoallergic chondrocytes were obtained from rabbit of 3 weeks old to culture in vitro, which were then transplanted to improved fibrin glue bracket for in vitro culture. Cells were divided into growth factor (GF) group, simple cytoskeleton group, simple bracket group as well as blank group. Cultured chondrocyte modules were randomly implanted into 48 3-month rabbit models of cartilage defect with 12 rabbits in each group to culture in vivo for 2-12 weeks. In vitro cell growth was observed and rabbits were executed respectively on the 2nd; 6th and 12th weeks of in vivo culture. The chondrocyte modules were histologically observed and scored in tissue engineering. Results: A total of 48 rabbits were involved in the analysis of results. (1) In vitro culture: The doubling time in simple cytoskeleton group was 5.0 days and that in multicellular growth factor culture system group was 3.8 days. There were significant differences in the growth velocity between the two groups. (2) In vivo culture: The repaired cartilage in cell growth factor group was closely integrated with adjacent cartilage with coincident thickness and the most cell number, which had better secretory capacity. The repaired cartilage in simple cytoskeleton group was not closely integrated with adjacent catilage with poor thickness and less cells, which had a certain secretory capacity. While those in simple bracket group were covered by fibrous tissue, and those in blank group were covered with noncohesive fibrous scar tissues and there were partial inflammatory cells. The score of tissue engineering was obviously better in the cell growth factor group than that in simple cytoskeleton group [blank group (10.94+/-1.77) points, simple bracket group (9.38+/-1.89) points,cytoskeleton group (7.31+/-1.54) points, growth factor group (3.81 +/-1.10) points, $P < 0.01$]. Multicellular growth factor could accelerate the proliferation of cartilage cells and formation of cartilage modules in tissue engineering in the construction of cartilage module for repairing defect in articular cartilage. Conclusion: Multicellular growth factor, working on the improved fibrin glue bracket can significantly accelerate the construction of compound and reparation of articular cartilage defection.

Full Text

Wound healing and degradation of the fibrin sealant Beriplast P following partial liver resection in rabbits.

Authors: Kroez M., Lang W., Dickneite G.

Publication Date: 2005

PMID: 40848026

Abstract

The objective of this study was to investigate the degradation kinetics of the fibrin sealant (FS) Beriplast P in an experimental liver surgery model in rabbits. A partial liver resection was performed in 21 rabbits, and the wound area covered with Beriplast P to ensure hemostasis. Wound healing of the resection sites was evaluated morphologically over 11 weeks. Degradation of the FS was evaluated by measuring the thickness of the remaining fibrin layer. Plasma samples were analyzed for antibodies against fibrinogen, albumin, thrombin, fibrin, and factor XIII. No postoperative hemorrhage was observed, indicating successful hemostasis throughout, The FS was degraded with a half-life of about 25 days postapplication and was completely replaced by granulation tissue within 9 weeks. The FS

degradation and tissue development followed the general stages of wound healing: inflammation and resorption, proliferation, organization and production of collagen, maturation, and scarring. An immune reaction was elicited against the main four human proteins of the FS. The antibody titers peaked on day 14, with a gradual decrease thereafter. We conclude that the FS accomplished hemostasis, facilitated healing in accordance with natural processes, and was completely degraded over time. In humans, the reduced immunogenicity of the FS would potentially increase its degradation half-life.

Full Text

Fibrin glue, healing of gastric mucosal injury, and expression of growth factors: Results from a human in vivo study.

Authors: Becker J.C., Beckbauer M., Domschke W., Herbst H., Pohle T.

Publication Date: 2005

PMID: 40462196

Abstract

Background: Fibrin glue is used in the endoscopic therapy of bleeding ulcerations. Accelerated closure of ulcers has been attributed to this treatment; the biologic reason, however, remains unclear. Methods: Two artificial gastric lesions were induced in healthy, Helicobacter pylori negative volunteers and were treated by injection of either saline solution or fibrin glue. After 72 hours, resulting ulcers were measured and biopsy specimens were taken for immunohistochemistry (to identify proliferating cells and small vessels) and assessment of growth factor messenger RNA (mRNA) expression (platelet derived growth factor, vascular endothelial growth factor, fibroblast growth factor 2 [FGF-2]) by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). Results: After 72 hours, most lesions exposed to fibrin glue were smaller than the corresponding ones treated with saline solution. The ulcer rim was more pronounced; immunohistochemistry revealed more proliferating cells ($p < 0.02$ compared with saline solution). The number of microvessels also increased, though this difference did not reach statistical significance ($p = 0.10$). FGF-2 mRNA expression markedly increased (about 7-fold compared with the control [$p < 0.001$], and about 5-fold compared with saline solution [$p < 0.015$]); whereas, with respect to platelet derived growth factor and vascular endothelial growth factor mRNAs, only small changes occurred. Conclusions: Fibrin glue positively modulates gastric ulcer healing by causing an increase in the number of proliferating cells in the ulcer margin and also possibly enhances the density of microvessels. These changes are accompanied by an enhanced expression of FGF-2, which is known to exert beneficial effects on ulcer healing. Copyright © 2005 by the American Society for Gastrointestinal Endoscopy.

Full Text

The study of a light-activated albumin protein solder to bond layers of porcine small intestinal submucosa.

Authors: Ware M.H., Buckley C.A.

Publication Date: 2003

PMID: 36433394

Abstract

This study investigated the feasibility of bonding layers of porcine small intestinal submucosa (SIS, Cook Biotech, Inc.) with a light-activated protein solder. SIS is an acellular, collagen-based extracellular matrix material that is approximately 100 mum thick. The solder consists of bovine serum albumin and indocyanine green dye (ICG) in deionized water. The solder is activated by an 808 nm diode laser, which denatures the albumin, causing the albumin to bond with the collagen of the tissue. The predictable absorption and thermal energy diffusion rates of ICG increase the chances of reproducible results. To determine the optimal condition for laser soldering SIS, the following parameters were varied: albumin concentration (from 30 - 45% (w/v) in increments of 5%), the concentration of ICG (from 0.5 -2.0 mg/ml H2O) and the irradiance of the laser (10 - 64 W/cm^2). While many of the solder compositions and laser irradiance combinations resulted in no bonding, a solder composition of 45% albumin, ICG concentration of 0.5mg/ml H2O, and a laser irradiance of 21 W/cm^2 did produce a bond between two pieces of SIS. The average shear strength of this bond was 29.5 +/- 17.1 kPa (n=14). This compares favorably to our previous work using fibrin glue as an adhesive, in which the average shear strength was 27 +/- 15.8 kPa (n=40).

Full Text

Fibrin sealants in supporting surgical techniques: Strength in factor XIII.

Authors: Phillips M., Dickneite G., Metzner H.

Publication Date: 2003

PMID: 36876113

Abstract

Factor XIII has a well-established role in natural coagulation and clot stabilization. It is often added back to fibrin sealants that are used in a wide range of surgical settings to achieve successful hemostasis, tissue adhesion and wound healing. Factor XIII is the final enzyme to be activated in the blood coagulation cascade. It plays an important role in maintaining the balance between coagulation and

fibrinolysis. Factor XIII facilitates the formation of covalent cross-links within the fibrin network, forming a loose mesh after activation by thrombin. It adds significant resilience to fibrin clots, augmenting strength by as much as 5-fold. Both fibrin cross-linking and the factor XIII-catalyzed ligation of the fibrinolysis inhibitor alpha2-antiplasmin to the fibrin clot contribute to the increased proteolytic resistance of factor XIII-stabilized clots. Preclinical studies indicate that the inclusion of factor XIII in fibrin sealants used for vascular grafting significantly reduces suture-hole blood loss. This has important implications for the successful control of bleeding in comparable clinical situations. The advantages of factor XIII stabilized clots (increased strength, resistance to proteolysis, promotion of wound healing) suggest that the presence of factor XIII in fibrin sealants may optimize their performance in the clinical setting. The aim of this paper is to review preclinical data that provide evidence for a potentially positive role for factor XIII in fibrin sealants.

Full Text

Fibrin sealants in supporting surgical techniques: The importance of individual components.

Authors: Wozniak G.

Publication Date: 2003

PMID: 36880778

Abstract

Fibrin sealants have many different uses across a broad range of surgeries, where they have proved successful in controlling bleeding, providing suture support and tissue sealing. The action of all fibrin sealants depends on the thrombin-catalyzed formation of a fibrin clot. However, neither the purity nor the concentration of the main components of fibrin sealants (thrombin and fibrinogen) is uniform across all commercial products and this will affect performance. In addition, the optional inclusion of other components such as factor XIII and antiproteolytic inhibitors may also influence the quality of clot formation. Properties that vary among different fibrin sealants, such as the clotting rate, viscosity, adhesiveness, clot strength and resistance to proteolysis, are all-important considerations for the surgeon. The application of fibrin sealants in a very wide spectrum of surgical procedures means that some fibrin sealants may be more suitable for a particular procedure than others. One of the advantages of commercial fibrin sealants is that the high level of quality control ensures that their composition is extremely consistent between batches. On the other hand, blood bank-derived fibrin sealants may vary in their composition from one preparation to the next and hence be less predictable in their performance. This paper discusses how individual components contribute to the overall performance of fibrin sealants, thereby providing to the surgeon the necessary information to select the optimal fibrin sealant for a specific procedure. © 2003 The International Society for Cardiovascular Surgery. Published by Elsevier Science Ltd. All rights reserved.

Full Text

Repair of calvarial defects with customized tissue-engineered bone grafts. I. Evaluation of osteogenesis in a three-dimensional culture system.

Authors: Schantz J.-T., Teoh S.H., Lim T.C., Endres M., Lam C.X.F., Hutmacher D.W.

Publication Date: 2003

PMID: 37046611

Abstract

Bone generation by autogenous cell transplantation in combination with a biodegradable scaffold is one of the most promising techniques being developed in craniofacial surgery. The objective of this combined in vitro and in vivo study was to evaluate the morphology and osteogenic differentiation of bone marrow derived mesenchymal progenitor cells and calvarial osteoblasts in a two-dimensional (2-D) and three-dimensional (3-D) culture environment (Part I of this study) and their potential in combination with a biodegradable scaffold to reconstruct critical-size calvarial defects in an autologous animal model [Part II of this study; see Schantz, J.T., et al. Tissue Eng. 2003; 9(Suppl. 1):S-127-S-139; this issue]. New Zealand White rabbits were used to isolate osteoblasts from calvarial bone chips and bone marrow stromal cells from iliac crest bone marrow aspirates. Multilineage differentiation potential was evaluated in a 2-D culture setting. After amplification, the cells were seeded within a fibrin matrix into a 3-D polycaprolactone (PCL) scaffold system. The constructs were cultured for up to 3 weeks in vitro and assayed for cell attachment and proliferation using phase-contrast light, confocal laser, and scanning electron microscopy and the MTS cell metabolic assay. Osteogenic differentiation was analyzed by determining the expression of alkaline phosphatase (ALP) and osteocalcin. The bone marrow-derived progenitor cells demonstrated the potential to be induced to the osteogenic, adipogenic, and chondrogenic pathways. In a 3-D environment, cell-seeded PCL scaffolds evaluated by confocal laser microscopy revealed continuous cell proliferation and homogeneous cell distribution within the PCL scaffolds. On osteogenic induction mesenchymal progenitor cells (12 U/L) produce significantly, higher ($p < 0.05$) ALP activity than do osteoblasts (2 U/L); however, no significant differences were found in osteocalcin expression. In conclusion, this study showed that the combination of a mechanically stable synthetic framework (PCL scaffolds) and a biomimetic hydrogel (fibrin glue) provides a potential matrix for bone tissue-engineering applications. Comparison of osteogenic differentiation between the two mesenchymal cell sources revealed a similar pattern.

Full Text

Fibrin glue for wound repair: Facts and fancy.

Authors: Clark R.A.F.

Publication Date: 2003

PMID: 38004417

Abstract

In wound repair, fibrin has a multiplicity of activities, some of which are intrinsic to the protein itself and some attributable to other blood constituents associated with the fibrin clot. Fibrin sealants, which have been approved for hemostasis in the US and Europe, are occasionally used wounds to promote healing. However, inconsistency exists in the literature regarding the benefit of these preparations in the healing process. Morecrude fibrinogen preparations, such as cryoprecipitates made from the patient's own blood on location, appear from the literature to have better utility in wounds than more purified fibrinogen preparations available through commercial sources. These divergent outcomes are likely attributable to additional blood-derived products being associated with cryoprecipitates compared to the relatively purified commercial fibrinogen preparations. Clearly standard preparations and methods of application of fibrin sealant need to be defined for each particular surgical setting to resolve the many ostensible discrepancies in the current literature. A corollary is that different fibrin sealant preparations are likely to be preferable for different clinical situations.

Full Text

Effectiveness of second-generation fibrin glue in endonasal operations.

Authors: Vaiman M., Eviatar E., Segal S.

Publication Date: 2002

PMID: 41123560

Abstract

We evaluated the efficacy and safety of the Quixil fibrin sealant after its application to endonasal operative sites. A total of 153 patients underwent nasal surgery. The rate of hemorrhagic complications was compared in the group with nasal packing and in the group in whom fibrin glue was used to stop postoperative bleeding. Our results indicate that the application of Quixil fibrin glue to the operative sites in various endonasal operations provides effective hemostasis and sealing. This fibrin glue is a more effective hemostatic agent than foam nasal packing and provides no complications, as can occur with packing. Patients with hypertension have no greater risk for postoperative bleeding if Quixil is used.

Full Text

The effect of TGF-beta2 in various vehicles on incisional wound healing.

Authors: Wright T.E., Hill D.P., Ko F., Soler P.M., Smith P.D., Franz M., Nichols E.H., Robson M.C.

Publication Date: 2000

PMID: 36882856

Abstract

BACKGROUND: The isoforms of transforming growth factor beta (TGF-beta) have been shown to be deficient in models of impaired wound healing. Exogenous application of the growth factor to enhance healing as been investigated. TGF-beta1 has been shown to enhance incisional wound strength, but to be dependent on the vehicle used to carry the cytokine. Because TGF-beta2 has shown safety in human trials of chronic wound healing, this study evaluates TGF-beta2 in acute incisional healing using a variety of vehicles. METHODS: Using an acute incisional wound model in healthy rats, rhTGF-beta2 was suspended in various vehicles including fibrin sealant (normal commercial concentration), fibrin sealant (dilute concentration), phosphate buffered saline/serum albumin, and a carboxymethycellulose gel. A single dose of the agent was instilled into the incisions at the time of wound closure and breaking strength analyses and histology performed periodically from days 3-14. RESULTS: TGF-beta2 enhanced the gain of incisional strength in all vehicles during the first two weeks of healing. This was most noticeable by day three with the carboxymethycellulose gel, but by day 7 with the other vehicles. Like reports with TGF-beta1, TGF-beta2 accelerated the gain of wound strength by about three days by day 11. Normal density fibrin sealant delayed incisional healing; whereas, the other vehicles without TGF-beta2 had no significant effect. CONCLUSIONS: The use of TGF-beta2 appears to be of value in increasing incisional wound strength in the first 14 days post-wounding in healthy rats and this effect is demonstrated in a variety of vehicles. These data support the hypothesis that the "normal" incisional wound healing curve can he shifted to the left. Shortening the time for gain of incisional wound strength may have potential clinical use.

Full Text

Optimization of laser-solder repair technique for possible application in strabismus surgeries.

Authors: Davis J.B., McNally-Heintzelman K.M.

Publication Date: 2002

PMID: 35005993

Abstract

Strabismus is the lack of binocular vision due to an inability to control one of the eye muscles. Corrective surgery is the most common recourse and consists of adjusting and reattaching the extraocular muscle to the sclera. In approximately 10% of cases involving re-insertment of the extraocular muscle via suture techniques, the needle is inserted too deeply into the eye resulting in perforation of the retina. Fibrin glues and cyanoacrylates have been substituted with unsatisfactory mechanical results. The goal of this study was to maximize the tensile strength of rabbit extraocular muscles repaired using a laser-solder technique developed by McNally et al., Biodegradable polymer

membranes of controlled porosity were fabricated with poly(L-lactic-co-glycolic acid) (PLGA) and salt particles using a solvent-casting and particulate-leaching technique. The porous membranes were doped with protein solder composed of 25 % and 50%(w/v) serum albumin and 0.5mg/ml indocyanine green (ICG) dye mixed in deionized water. In vitro tissue specimens were repaired using the solder-doped polymer membranes in conjunction with an 805nm diode laser. The tensile strength was tested on an MTS machine and results were analyzed with the Student's T-test.

Full Text

Wound healing: Role of commercial fibrin sealants.

Authors: Amrani D.L., Diorio J.P., Delmotte Y.

Publication Date: 2001

PMID: 32613943

Abstract

This paper focuses on the use of commercial fibrin sealant (FS) in specific wound healing applications. This review is not intended to be all inclusive, but to examine in vitro and in vivo models, as well as select clinical conditions that are representative of specific wound healing applications of FS.

Full Text

Biological wound tissue glue systems in wound healing. [German]

Authors: Stark G.B., Horch R.E., Voigt M., Tanczos E.

Publication Date: 1998

PMID: 129389353

Abstract

Tissue engineering relies on in vitro cell culture, biocompatible matrix materials and genetic engineering with growth and differentiation factors for guided tissue regeneration. Biogenic or semisynthetic biomaterials are an alternative as cell carriers: To circumvent the disadvantages of conventional keratinocyte sheet grafts, a keratinocyte fibrin glue suspension KFGS (H. W. Kaiser et al., Burns 20: 23, 1994), which mainly consists of epidermal stem cells, has been tested experimentally in nude mice and clinically in extensive burns and chronic wounds. In the "in vivo culture" on the wound, the non-confluent keratinocytes form a differentiated epithelium within days. Current research aims at guided dermal regeneration by a combination with allodermis or biomaterials (collagen sponges like

TissueFaszie, Microspheres etc.). Fibrin glue (Tissuecol) has also been tested successfully as matrix for other cells like chondrocytes and fibroblasts transfected with growth factor genes (EGF/KGF).

Full Text

Histomorphological evaluation of wound healing of rabbit oviduct after microsurgical reanastomosis with the use of autologous fibrin adhesive, human fibrin adhesive or poly-glycolic acid suture.

Authors: Weis-Fogh U.S., Pedersen H., Schroeder E., Sorensen S.S., Olesen H.P.

Publication Date: 1993

PMID: 23238932

Abstract

The morphology of the healing process of microsurgical reanastomosis of the rabbit oviduct with the use of fibrin adhesive, autologous and heterologous, and conventional sutures is described. Both oviducts in 48 rabbits were cut and reanastomoses were performed. The rabbits were killed at different intervals after the operations, ranging from 2 h to 28 days, and the anastomoses were evaluated by histomorphological examination. The autologous fibrin adhesive was absorbed after a week and an uncomplicated healing was observed. Heterologous fibrin adhesive caused a granulomatous inflammation interpreted as an immune reaction of the host to the foreign protein, and conventional suturing resulted in severe tissue damage with an intensive inflammatory reaction.

Full Text

Local application of BMP-2 specific plasmids in fibrin glue does not promote implant fixation.

Authors: Faensen B, Wildemann B, Hain C, Hohne J, Funke Y, Plank C, Stemberger A, Schmidmaier G

Publication Date: 2011

PMID: 21762501

Abstract

BACKGROUND: BMP-2 is known to accelerate fracture healing and might also enhance osseointegration and implant fixation. Application of recombinant BMP-2 has a time-limited effect.

Therefore, a gene transfer approach with a steady production of BMP-2 appears to be attractive. The aim of this study was to examine the effect of locally applied BMP-2 plasmids on the bone-implant integration in a non-weight bearing rabbit tibia model using a comparatively new non-viral copolymer-protected gene vector (COPROG). METHODS: Sixty rabbits were divided into 4 groups. All of them received nailing of both tibiae. The verum group had the nails inserted with the COPROG vector and BMP-2 plasmids using fibrin glue as a carrier. Controls were a group with fibrin glue only and a blank group. After 28 and 56 days, these three groups were sacrificed and one tibia was randomly chosen for biomechanical testing, while the other tibia underwent histomorphometrical examination. In a fourth group, a reporter-gene was incorporated in the fibrin glue instead of the BMP-2 formula to prove that transfection was successful. RESULTS: Implant fixation strength was significantly lower after 28 and 56 days in the verum group. Histomorphometry supported the findings after 28 days, showing less bone-implant contact.In the fourth group, successful transfection could be confirmed by detection of the reporter-gene in 20 of 22 tibiae. But, also systemic reporter-gene expression was found in heterotopic locations, showing an undesired spreading of the locally applied gene formula. CONCLUSION: Our results underline the transfecting capability of this vector and support the idea that BMP-2 might diminish osseointegration. Further studies are necessary to specify the exact mechanisms and the systemic effects.

Full Text

['BMP-2 is known to accelerate fracture healing and might also enhance osseointegration and implant fixation. Application of recombinant BMP-2 has a time-limited effect. Therefore, a gene transfer approach with a steady production of BMP-2 appears to be attractive. The aim of this study was to examine the effect of locally applied BMP-2 plasmids on the bone-implant integration in a non-weight bearing rabbit tibia model using a comparatively new non-viral copolymer-protected gene vector (COPROG).', 'Sixty rabbits were divided into 4 groups. All of them received nailing of both tibiae. The verum group had the nails inserted with the COPROG vector and BMP-2 plasmids using fibrin glue as a carrier. Controls were a group with fibrin glue only and a blank group. After 28 and 56 days, these three groups were sacrificed and one tibia was randomly chosen for biomechanical testing, while the other tibia underwent histomorphometrical examination. In a fourth group, a reporter-gene was incorporated in the fibrin glue instead of the BMP-2 formula to prove that transfection was successful.', 'Implant fixation strength was significantly lower after 28 and 56 days in the verum group. Histomorphometry supported the findings after 28 days, showing less bone-implant contact.', 'In the fourth group, successful transfection could be confirmed by detection of the reporter-gene in 20 of 22 tibiae. But, also systemic reporter-gene expression was found in heterotopic locations, showing an undesired spreading of the locally applied gene formula.', 'Our results underline the transfecting capability of this vector and support the idea that BMP-2 might diminish osseointegration. Further studies are necessary to specify the exact mechanisms and the systemic effects.', 'Total hip and total knee arthroplasties (THA, TKA) in the industrialized countries are increasing and demographic data suggest that this progress is going to continue [1-3]. According to the Swedish National Total Hip Arthroplasty Register with more than 270,000 registered THA from 1979-2006, the leading cause for component failure in THA is aseptic implant loosening [4]. Besides osteolysis due to wear debris (especially of polyethylene components) it is assumed that a lack of initial bony incorporation of the implant favors aseptic loosening. Bone ingrowth does not occur properly if micromotion exceeds 150 μm [5]. Therefore, many attempts have been made to improve the incorporation of the implant. The design of the prosthesis has a large impact on primary stability. Modifications to the implant surface, such as different micro- and macrostructures or osteoconductive coatings (e.g. hydroxylapatite), have shown to play a decisive role in improving primary as well as secondary stability, due to bone ingrowth [6-8].', 'It is well accepted that certain growth factors (GF), mostly members of the transforming growth-factor superfamily, i.e. bone morphogenetic proteins (BMP) and transforming growth factor β (TGF-β) promote bone formation [9-11]. BMP-2 is well known to have high osteoinductive potency and to improve bone healing. In the last years, clinical application of BMPs has become common in the treatment of atrophic non-unions of

shaft-fractures, open tibial fractures and spine-fusions[10]. In experimental studies also the improvement of implant incorporation into bone has been shown under the influence of BMP-2 [12,13] as well as of BMP-7 [14,15].', 'Regardless of the indication, providing a steady long-term delivery of recombinant growth factors to the site of action remains an unsolved problem. Therefore, the idea of a gene transfer system to establish a constant long-term but still temporally controlled local level of GF at the wound site appears to be an attractive method.', 'Gene therapy aims at the replacement of a defective or missing gene or at the additional insertion of an existing gene to start or stimulate the production of a certain gene product, e.g. a growth factor.', 'A vector is needed to insert the gene into a target cell. This vector is either of viral origin or it is a so called non-viral vector. In the latter group, a variety of techniques are used, including synthetic molecules or physical methods. A vector should have properties which enable it to carry the gene to the target cell and to invade the cell. Non-viral vectors generally show a relatively poor potency in introducing nucleic acids into cells (transfection) compared to viral vectors, where the introduction of nucleic acids into cells (transduction) is part of the natural viral life cycle. On the other hand, non-viral vectors are accepted to be safer than their potentially mutagenic or immunogenic viral counterparts [16,17].', 'The aim of this in vivo study was to investigate the influence of a plasmid encoding BMP-2 on implant incorporation in a non-weight bearing rabbit model. In addition we studied the effectiveness of the promising, comparatively new (non-viral) copolymer-protected gene vector (COPROG) [18,19] as well as safety aspects.', 'All animal studies were approved by the proper authorities (Landesamt für Arbeitsschutz, Gesundheitsschutz und technische Sicherheit Berlin, Germany).', 'Sixty male New Zealand White rabbits (Harlaan-Winkelmann, Germany) with an average age of 8 months underwent surgery.', 'As a carrier for the vector formula, we used commercially available two component fibrin glue. Once bonded, the glue would keep the drug formula at the wound site. It has been proven that the incorporation of the plasmid formula does not change the properties of the glue, so that in can be applied as intended by the manufacturer [20].', 'An established animal model was chosen for the in vivo experiments. The rabbit tibia allows an easy surgical approach and the possibility to transfect bone tissue in New Zealand White Rabbits has already been shown before [21].', 'The animals were divided in 4 groups. All animals received anterograde intramedullary titanium nails (2.5 mm diameter) in both tibiae. A common two-component fibrin sealant (Tissucol®, Baxter, Germany) was used as drug carrier, which was injected into the reamed tibia (2.8 mm) before inserting the nail. The fibrinogen component carried the gene vector.', 'There were three groups of 16 animals each and one group of 12 animals: 1. a control group which received the nail only, 2. a second control group (fibrin glue group) which received the nail with fibrin glue but without plasmids, and the 3. the verum group, received the nail with fibrin sealant and the plasmids. Half of the animals of each group were sacrificed after 28 days and the other half after 56 days. The tibiae of each animal were randomly assigned for either histomorphometry or biomechanics. In the fourth group, 12 animals served as the reporter-gene control group and the animals were sacrificed at 4, 7 and 28 days. Luciferase, an enzyme normally only expressed by the firefly, was used as the reporter-gene.', 'The non viral vector used in this study is a Copolymer Protected Gene Vector (COPROG). It consists of a positively charged polycation-Plasmid DNA polyplex coated by a protective anionic peptide-PEG copolymer (PROCOP), which diminishes the susceptibility of the complex to aggregation, to complement activation and interaction with serum proteases [18]. The non viral vector, provided in lyophilized form can easily be incorporated in the fibrin-component of the fibrin glue. In the verum group, it carried 84 micrograms of a plasmid encoding for human BMP-2 (pB-BMP-2). In the Luciferase group, the glue was carrying a plasmid encoding for the reporter-gene Luciferase (pCMV-luc). The plasmids were also provided by the Institute of Experimental Oncology, TU München, Germany. The amount of 84 micrograms of plasmid/implant is based on the manufacturing procedure of the plasmid/COPROG-mixture and represents the highest possible "load" of COPROG to the fibrin component without compromising the maximum clotting firmness (MCF) of the fibrin glue.', 'After the animals were anaesthetized with Ketamine (90 mg/kg body-weight) and Medetomidine (0.04 mg/kg body-weight) both hind legs were shaved. Animals were weighed, intubated and received analgesia with Buprenorphine (0.3 ml i.m.). Perioperative antibiotic prophylaxis with Enrofloxacine s.c. was given immediately before the operation; inhalative narcosis was maintained with isoflurane.', 'During the initiation of anaesthesia, the lyophilized COPROG-formula was mixed with the thrombin component of

the fibrin glue. The operation was executed under sterile conditions. After incision of the tibia, a hole of 3.2 mm diameter was drilled into the corticalis medial to the tuberosity. Subsequently, the medullary cavity was reamed first with a 2 mm hand brace, followed by 2.5 mm and 2.8 mm. After measuring the length of the tunnel, Titanium Elastic Nails (Synthes, Switzerland) of 2.5 mm diameter were cut for later insertion. In all groups except for the blank group, approximately 0.3 ml fibrin glue was injected into the reamed marrow. The fibrinogen component was injected first, followed by the thrombin part, carrying 200 μg of COPROG containing 84 μg of BMP-2 plasmid in the verum group or Luc-Plasmid in the Luciferase group. After that the implant was inserted in anterograde direction (Figure 1). In all animals, both tibiae were operated the same way. After radiographic control of the correct position of the nail, the wound was closed in layers. Postoperative analgesia with Buprenorphine i.m. was given for 2 days.', 'X-ray of the tibia postoperatively (a) a.p.-view (b) lateral view.', 'Radiographs were taken postoperatively and after the animals were sacrificed, using standardized settings.', 'Animals were sacrificed 28 days and 56 days after surgery by intravenous injection of potassium chloride after anaesthesia with Ketamine and Medetomidine. Both tibiae were explanted and randomly assigned for the biomechanical testing or prepared for histomorphometric examination.', 'The biomechanical setup was designed to measure the strength of the attachment of the implant-bone interface. Therefore, we used a push-out device described by Schmidmaier et al. 2002 [22], modified for the bigger rabbit tibia. After cutting off the distal and proximal epiphysis, the bones were prepared carefully in order to reveal about 4 mm of the nail at the distal and proximal end. Subsequently, the tibia was inserted into the testing device and the distal part of the diaphysis was embedded into methyl-metacrylate (MMA). After the cement hardened, the device was positioned into a material testing machine (Zwick, Germany). The machine applied a constant linear anterograde force at a rate of (2 mm/min.) onto the nail and the force was measured and transferred to a computer. The maximum force at ultimate failure was used as parameter for the bone-implant attachment strength. To avoid impreciseness caused by different length of the bones the peak force was set in ratio to the total bone area surrounding the implant. The biomechanical testing resulted in a typical curve with a sharp peak, expressing the force needed to loosen the implant (Figure 2).', 'A typical load-displacement curve with a peak at 72 N, describing the force needed to loosen the nail.', 'The contra-lateral tibiae were prepared for histomorphometrical examination:', 'After explantation, the proximal and the distal epiphysis were removed to enable the fixation solution (10% normal buffered formaldehyde) to infiltrate into the whole specimen. Specimens were kept in the solution for 5 days followed by dehydration in ethanol of ascending concentrations. Specimens were then embedded in methyl- metacrylate (Technovit 7200, Heraeus-Kulzer, Germany). After polymerization, the resulting blocks including the specimens were cut in longitudinal direction using a cutting device (Exakt, Germany). They were then ground using a grinding device (Exakt, Germany) until the whole specimen could be detected on the surface showing the maximum implant diameter of 2.5 mm. The ground blocks showing the specimens were glued to a microscope slide. The upper parts of the blocks were removed using a diamond band saw (Exakt, Germany), leaving slides of approximately 300 μm of MMA including the specimens. These slides were ground down to 80 μm and staining was performed with Safranin-O and van Kossa. For the histomorphometric analysis, the entire specimen was scanned using a motorized stage with a 10 x objective and a digital camera attached to a microscope (Leica DM-RB, Leica, Germany). The digital pictures were combined with the use of a computer-software (Mosaix, Zeiss, Germany).', 'To define the bone-implant contact as a sign of integration, the length of all sections where bone was tangent to the implant was measured and set as a ratio to the entire implant length, resulting in a percentage of implant surface covered by bone. The analysis differentiated between direct bone contact, where calcified tissue was directly adjacent to the implant and indirect contact, where bone had grown close to the implant, but a gap was visible (see Figure 3).', 'Histologic preparation stained with Safranin-O/van Kossa. Blue circles are marking a zone of direct bone contact, the yellow circle marks a zone of indirect bone contact.', 'In the Luciferase group, where a plasmid encoding for Luciferase replaced the BMP-2 encoding plasmid, animals were sacrificed at days 4, 7 and 28. Tissue from the operated tibiae, brain, lungs, liver, spleen, testicles and muscle was taken. Also bone samples from the not operated forelegs were analyzed. The bone was grinded with a cooled grinding device before processing. For analysis, the tissue of the parenchymatous organs was homogenized and lysed.', 'Total RNA was extracted using „RNeasy" Kit®

(Quiagen, Germany). Concentration and purity was determined photometrically at 260/280 nm. Approximately 80 ng of total RNA were used for Reverse Transcription PCR. Thereby, single-stranded mRNA was transcribed into complementary DNA (cDNA). In the following non-quantitative PCR the luciferase transcripts were amplified with specific luciferase primers (f 5' ctg aat aca aat cac aga atc gtc g 3'; r 5'aaa tcc ctg gta atc cgt ttt aga 3'). Additionally, the housekeeping gene GAPDH (Glyceraldhyde-3-phosphate-Dehydrogenase) was amplified (f 5'gca tgt cag atc cac aac gga t 3'; r 5'tgt cag caa tgc atc ctg ca 3'). All PCR products were detected on 1.5% agarose gel (Serva) with Ethidiumbromide (Merck, Germany).', 'Animals were randomized in a blinded manner by drawing lots before the operation. The tibiae (right or left) were also randomized for histological and biomechanical investigation.', 'To determine statistically significant differences in the histomorphometrical and biomechanical results, a Kruskal Wallis followed by Mann-Whitney Test and Bonferroni Holm correction was used (SPSS 14.0, SPSS Inc., Chicago, USA).', 'One animal of the 28 days Luciferase group died during anaesthesia and was excluded from the study. A connection to the vector administration could not be found. All other animals tolerated the procedure well.', 'Neither the clinical appearance nor the blood specimens suggested an infection at the wound site. In some animals, a transient swelling at the nail insertion site was observed.', 'Radiographs showed that the implants were correctly positioned and had a similar fitting in all animals. No dislocations, fractures, or other abnormalities were observed postoperatively or after scarifying. Radiographic analysis did not reveal any difference between the groups at any of the time points.', 'Similar to the radiographic examination, gross observation revealed no fractures or abnormalities to any of the bones. Throughout the groups, the recording of the testing process showed a typical load-displacement curve with a steep start and a peak, when the force needed to loosen the implant had been reached (Figure 2). The peak force was set in relation to the length of the tested bone to compensate for differences in length between the specimens. In the blank control group an increase in the strength of fixation was detectable between day 28 and 56. This increase in implant fixation over time was less pronounced in the two other groups. The strength of fixation was significantly lower in the verum group at both time points compared to the blank control group. The difference between the blank control group with no filling of the medullar cavity and the fibrin glue group was not significant at either of the time points (Figure 4).', 'Shear forces needed to loosen the implant. Highest results were found in the control group after 56 days. *a p = 0.001 *b p = 0.005 *c p = 0.002. The boxes show the 25th and 75th percentile and the band in the box is the 50th percentile (the median). The whiskers represent the minimum and maximum of all the data.', 'At day 28 after operation, the measured direct and indirect bone implant-contact was greatest in the blank control group. The fibrin glue group showed almost the same results for direct contact as for indirect contact. The verum group showed significantly lower direct and indirect contact compared to the other groups. These findings support the biomechanical results after 28 days, where the verum group showed significantly lower strength of fixation compared to the other groups.', 'After 56 days, the results of the verum group were highest regarding the direct bone-implant contact, but did not differ significantly from the blank control group. Indirect contact was comparable in both groups. The fibrin glue group showed the least amount of direct contact after 56 days, while the indirect contact did not differ significantly after 56 days (Figure 5).', 'Direct and indirect bone-implant contact. a) Direct bone-implant contact: after 28 days significantly less direct contact in the BMP-2 plasmid group. After 56 days the results were comparable in all groups. b) Indirect bone-implant contact. Also, significantly less in the BMP-2 plasmid group after 28 days. After 56 days, again comparable results of all groups. *a p = 0.02 *b p = 0.001. The boxes show the 25th and 75th percentile and the band in the box is the 50th percentile (the median). The whiskers represent the minimum and maximum of all the data.', 'One animal of the Luciferase group died during anaesthesia.', 'In 20 of the 22 explanted tibiae Luciferase was detected. In two animals Luciferase could only be found in one of the two tibiae (one of the 4 days group and one of the 28 days group). This means that transfection was successful in 90.9%.', 'Independent of the time point, luciferase-RNA could be detected after 4, 7 and 28 days. Thus demonstrating a successful transfection had been achieved.', 'However in the majority of animals, luciferase-RNA was also found in other tissues besides the treated tibiae. There was no obvious relationship between time points and detection of luciferase-RNA, transfection of heterotopic organs took place without any pattern throughout all groups (Table 1).', 'Results of the Luciferase mRNA detection in bone and other organs',

'Detection of Luciferase mRNA in bone and other organs Number and kind of tissue in animals being positive for Luciferase RNA in heterotopic organs. pos. = positive signal, (pos) = weak signal, neg. = no signal.', 'Accelerated and improved implant integration could have a significant impact on implant survival, reduction of hospitalization and patient satisfaction. Several authors have described improved bone-implant healing using recombinant BMP-2 or other BMPs [23-25]. Gene therapy offers a promising alternative to the direct application of a recombinant protein by stimulating local target cells to produce more of a desired product, e.g. a growth factor for a period of time that lasts longer than a single application of a recombinant protein. A vector is needed to deliver the genetic information into the target cell. Subsuming the differences between viral vectors and non-viral methods, it is most important that non-viral vectors are unable to match viral vectors concerning their potency in transfecting the target cells. On the other hand, viral vectors are believed to be not as secure, i.e. being more at risk to cause problems due to immunogenicity or mutagenicity, whereas non-viral vectors are believed to be safer. Unlike in systemic genetic disorders where one might want to transfect a majority of target cells of an individual by a systemic application of a gene formula, in the case of tissue repair or regeneration only a local effect is required and desired. A systemic transfection of cells would be an intolerable safety issue. In this study it could be proven that a gene transfer using the non-viral gene vector COPROG was achieved. Transfection could be confirmed by detecting the Luciferase reporter-gene via rtPCR in the operated tibiae. Luciferase RNA could be found in all of the 11 animals included in the reporter-gene groups.', 'The biomechanical results did not meet the expectations concerning the effect of BMP-2. A significantly weaker implant incorporation was measured at 28 and 56 days after surgery when the BMP-2 plasmid was used. This result corroborates the belief that BMP-2 under certain conditions is also capable of impairing bone formation rather than enhancing it. In recent years, many studies have shown the potency of BMP-2 to promote bone healing. BMP-2 is commonly used clinically to accelerate bone healing after fractures or in cases of non-union as well as in spinal fusion. Some experimental studies showed an improved bone-implant interface through the use of recombinant BMP-2 protein [12,13]. However, there are reports that the effect of BMP-2 can differ fundamentally as the protein is not only capable of enhancing bone formation but also of promoting its degradation by stimulating osteoclasts [26-28]. The circumstances under which the resorption is more pronounced than the bone formation in vivo is not yet clear. In 1996 Jepsson et al. found unexpected inhibitory effects of BMP-2 on bone formation in an established rabbit model. The experiment was repeated in 1999 with variations in dosage, type of BMP and other experimental design modifications. The inhibitory effect was a consistent finding but a mechanism responsible for it could not be determined0[29]. Sena et al. found a dosage dependent negative effect of TGF-ß2 on strength of fixation and bone/implant contact in a well established rat model. Interestingly, the bone volume was increased in the TGF-ß2 treated animals [30]. Stadlinger et al. ruled out a detrimental effect of BMP-4 on implant integration in a miniature-pig model when different surface modifications of collagen, collagen and chondroitin sulfate and collagen, chondroitin sulfate and BMP-4 were compared [31]. Liu et al showed in a pig model that different modes of delivery for BMP-2 change the osteoconductivity of surfaces. Different surfaces (metal with/without CaP coating) with or without incorporated or absorbed BMP-2 were investigated. New bone formation was highest in the coated and uncoated groups bearing no BMP-2 followed by the groups where BMP-2 was incorporated in a coated surface. The lowest results concerning deposited bone were found in the coated implants bearing only adsorbed BMP-2. As a second parameter in the study of Liu et al. the interface coverage with bone was examined. This was found highest for blank coated implants, followed by coated implants bearing incorporated or incorporated and adsorbed BMP-2. The lowest results were found in the uncoated implants bearing adsorbed BMP-2. The authors conclude, that osteoconductivity of an implant surface can be significantly influenced not only by BMP-2 but also by the mode of delivery [32]. Egermann et al. found a systemic inhibition of bone formation in a sheep model after local application of adenoviral vectors encoding BMP-2. The effect could be detected by a micro-CT scan 8 weeks after creating standardized defects of the iliac crests on both sides and unilateral local application of Ad.BMP-2. The effect might have been connected to an increased inflammatory response since the histological analysis showed an elevated level of inflammatory cells at the treated bone defects [33]. All these findings and the results of our study are in contrast to the generally accepted positive impact of BMP-2 in fracture healing.

Possibly the unexpected effects seen in our present study also can be explained by the different ways new bone is formed during secondary fracture healing and implant integration. While in fracture healing bone formation usually happens via a chondrogenesis and endochondral ossification, unless anatomical repositioning is achieved, implant integration occurs via [34]. BMP-2 is known to promote an endochondral ossification pattern [35], which could interfere with the primary bone-implant healing process and by this account for the poor results of the groups treated with BMP-2 plasmids compared to the other groups.', 'The histological findings at day 28 supported the biomechanical results. The BMP-2 plasmid group showed the least direct and indirect bone contact. At day 56 the biomechanical results were lowest for the BMP-2 plasmid group while the histomorphometry showed comparable direct bone-implant contact and indirect bone-implant contact in all three groups, not elucidating the biomechanical findings. Further conclusions how the weak implant healing connects to the comparatively large bone-implant contact zone could not be drawn from this experimental design.', 'In a recent study Sena et al. saw a dose dependent lowering of bone implant contact and fixation strength in a similar model, using a rat femur and different dosages of rhTGFß [30]. In this study, rhTGFb enhanced bone formation at dosages of 5, 10 and 20 micrograms/implant, while at the same time all concentrations of rhTGFß lowered the bone-implant contact and fixation strength. The authors concluded that for fixation strength the location of bone formation is also important, in addition to the amount of bone formation. These findings correlate with our results. Despite a comparable bone-implant contact at day 56, we did not see an improvement in fixation strength.', 'In the Luciferase group the reporter gene Luciferase could also be found irregularly distributed in heterotopic organs in 10 out of 11 animals. The application of the COPROG/fibrin mixture had been performed with a great deal of caution in order not to spread the formula elsewhere than the wound site. Therefore, the most reasonable explanation for the contamination might be the systemic spread of the locally applied COPROGs due to the rising of the intramedullary pressure during the insertion of the implant. By this, vector loaded fibrin particles might have been pushed into the venous vessels of the tibial bone leading to a systemic distribution of the COPROGS - comparable to the pathogenesis of fat embolism during intramedullary nailing or total joint arthroplasties. Of the systemically transfected organs, muscle tissue showed by far the lowest transfection rate. It could only be found in 1 animal of the 4-day group.', 'In summary, it could be proven that transfection using the copolymer protected gene vector was achieved, however without a stimulation of implant integration due to the BMP-2 plasmid application. The systemic distribution of the vector, as we found in our reporter gene groups, is not desired and demands further improvement. Fibrin glue as a drug carrier was chosen to release the plasmid formulation due to degradation of the fibrin matrix. This mechanism had been described earlier[20]. The gene-therapeutic approach was used to provide a steady production of BMP-2 at the wound site. Our study supports findings that under certain circumstances BMP-2 might impair implant integration. This work was targeted as a proof of concept study and therefore has limitations in providing information about the exact mechanisms which led to the observed results, e.g. a possible dose-dependent effect of BMP-2. But in this study the proof of transfection in a large animal model using the non-viral vector COPROG could be demonstrated for the first time. The systemic effect means a security risk on the one hand, but shows the capacity of the formula to not only act locally.', 'The author declares that they have no competing interests.', 'BF was the surgeon who carried out the operations. He took part in designing the study and was responsible for the biomechanical testing and the preparation of histological specimens.', 'BW took part in designing the study and performed the statistical analysis. CH, JH and YF assisted in the surgical procedures and were responsible for animal care. CH mainly contributed to the histological examinations, JH carried out the biomechanical studies and YF was responsible for the PCR assays. CP and AS were in charge of the production of the gene vector. GS designed the study for the most part and was responsible for the coordination between the study groups in Berlin and Munich.', 'All authors read and approved the final manuscript.', 'The pre-publication history for this paper can be accessed here:', '://www.biomedcentral.com/1471-2474/12/163/prepub', 'This study was funded by a grant from the Deutsche Forschungsgemeinschaft (DFG, Schm 1436/5-1) and by a grant from the German Federal Ministry of Education and Research (0312019A and 0312019C).', 'The author would like to thank Dr. Bettina Willie for revising the manuscript in terms of language corrections.']

Successful endoscopic clipping and application of fibrin glue for an esophago-mediastinal fistula after an esophagectomy.

Authors: Makino H., Miyashita M., Nomura T., Hagiwara N., Takahashi K., Matsuno K., Sumiyoshi H., Iwamoto M., Yokoi K., Uchida E.

Publication Date: 2011

PMID: 51278150

Abstract

A 64-year-old man visited our hospital complaining of abdominal discomfort. A 2-cm-long 0-IIc + IIa esophageal superficial carcinoma was detected in the middle third of the thoracic esophagus with endos-copy and esophagography. Computed tomography (CT) did not detect any metastasis. The patient underwent videoassisted thoracic surgery of the esophagus (VATS-E). Anastomotic leakage and a thoracic abscess were detected 16 days after the operation. Repeated thoracic drainages and conservative therapy with enteral nutrition were continued for approximately 1 month, but an esophago-mediastinal fistula and small mediastinal cavity remained. Additional drainage using interventional radiology (IVR) reduced the size of the cavity, but could not cure the esophago-mediastinal fistula, 68 days after the operation. The occurrence of an esophago-respiratory fistula followed by a thoracic abscess is a very serious and frequently fatal complication. We performed endoscopic clipping and filling with fibrin glue and succeeded in closing the fistula. Oral intake was started after training in swallowing, and the patient was discharged from hospital 172 days after the operation. One year after the operation he has no sign of a recurrence of the tumor or fistula. We demonstrated a case in which an esophago-mediastinal fistula was successfully repaired by endoscopic clipping with fibrin glue after an operation.

Full Text

The use of fibrin glue to prevent seroma formation following sentinel node biopsy [3] (multiple letters).

Authors: Falworth M.S., Butler P.M., Powell B.W.E.M., Silverman R.P., Elisseeff J., Passaretti D., Randolph M.A., Yaremchuk M.J.

Publication Date: 1999

PMID: 29566042

Abstract

Not Available

Full Text

Laboratory indicators of the efficiency of fibrin glue in laparoscopic surgery.

Authors: Stanojkovic Z., Antic A., Stanojkovic M., Jelic M., Dencic S., Sokolovic D.

Publication Date: 2014

PMID: 71556591

Abstract

BACKGROUND: Fibrin glue (FG) is a blood-derived tissue adhesive that mimics the natural coagulation process. It consists of two basic components - fibrinogen and thrombin, where activation of fibrinogen and its transformation into fibrin under the action of thrombin is the third phase of blood coagulation. FG is used to promote wound healing, skin grafting, to provide hemostasis in microvascular surgery and parenchymal injury and to serve as a matrix for repair of bone defects. The aim of this study was to analyze laboratory indicators of the metabolic response to surgical trauma, when applying different means of hemostasis during laparoscopic cholecystectomy. METHODS: The study included a total of 40 experimental pigs in which was performed laparoscopic cholecystectomy and intraoperative artificially damage of gallbladder boxes, which was repaired using FG in animals of experimental group (EG) or using standard means in animals of the control group (CG). FG was homemade, prepared from two components, of which the first was prepared from the cryoprecipitate with the addition of antifibrinolytic agents (aprotinin). The second component was a commercial bovine thrombin with calcium chloride. During 30 days of follow-up we have taken blood samples for following biochemical tests: general laboratory tests (glucose, bilirubin, cholesterol, triglycerides), enzyme markers of hepato-biliary damage (AST, ALT, AP, GGT), parameters of synthetic liver function (total protein and albumin), electrolytes (Na, K). RESULTS: There is a statistically significant higher levels of AST and ALT in CG ($p<0,05$), while the level of GGT and AP is less in EG from the fifth to thirtieth day, but without statistical significance. The elevated values of AST and ALT in EG faster return to normal (day 5th in EG vs day 14th in CG). Postoperative concentration of Na+ does not show a statistical difference between groups, while the concentration of K+ in CG is high statistical decreased until the 14th day (3,725+/-0,386 in CG vs 5,025+/-1,237 in EG, $p<0,0001$). CONCLUSIONS: Application of FG provides less parenchyma destruction and faster liver recovery and thus can be used as efficient hemostatic agent in laparoscopic surgery.

Full Text