

The state of the art of human hemoderived surgical glue

Angelica Tibola¹ & Luciana Grazziotin Rossato¹.

¹Instituto de Ciências Biológicas, Curso de Farmácia, Universidade de Passo Fundo BR 285, Km 171, Bairro São José, Passo Fundo, Rio Grande do Sul, Brasil - CEP 99052-900. Fone/Fax: 55 (54) 3316-8499

*Autor correspondente: Luciana Grazziotin Rossato. E-mail: (luciana.g.rossato@gmail.com).

Resumo

A cola de fibrina (CF) e o plasma rico em plaquetas (PRP) surgiram como métodos alternativos de restabelecimento da hemostasia para substituir a sutura tradicional. O objetivo do trabalho foi revisar a literatura sobre a utilização, produção e desenvolvimento da CF e do PRP. A busca de artigos realizou-se nas bases de dados Scielo, Pubmed e LILACS, utilizando como palavras-chave “CF”, “gel de plaquetas (GP)”, “selante de fibrina”, “PRP” e os seus equivalentes em inglês. Foram ponderados os artigos publicados a partir de 2009. A CF mostrou ser muito eficaz na área oftalmológica, melhorando também a fixação de malha para correção de hérnia inguinal. Já em artroplastia de joelho é uma opção para reduzir a perda sanguínea, porém na literatura nem todos os resultados são unânimes. O PRP é considerado eficaz para melhorar a cicatrização de enxertos cutâneos e promover a reversão de processos degenerativos no caso da fascite plantar. A aplicação da CF e do PRP é crescente e apresenta várias vantagens. Considerando o GP e o PRP, mais estudos são necessários visando padronizar as técnicas de obtenção e concentração plaquetária, ótima para a atividade selante destas colas hemoderivadas.

Palavras-chave: Adesivo tecidual de fibrina, Coagulação sanguínea, Hemostasia, Plasma rico em plaquetas, Técnicas de sutura.

Abstract

The fibrin glue (FG) and platelet rich plasma (PRP) have emerged as alternatives to replace traditional suture. The aim of the present work was to review the current literature about the use, production, and development of FG and PRP. This research was performed in SciELO, PubMed and LILACS databases using the keywords “fibrin glue”, “platelet gel”, “fibrin sealant”, “platelet rich plasma”, and their Portuguese equivalents. Only manuscripts published after 2009 were considered. The FG has proved to be very effective in ophthalmic procedures and in the treatment of inguinal hernia. Regarding, knee arthroplasty, despite controversies, CF is an option to reduce blood loss. The PRP was considered effective for improving healing of skin grafts and promoting the reversal of degenerative processes in case of plantar fasciitis. The application of CF and PRP is growing and has several advantages. Considering the platelet gel and the PRP, further studies are needed to standardize the experimental protocols to obtain PRP and to validate the optimal platelet concentrations to improve the function of these hemoderived-sealant adhesives.

Keywords: Fibrin Tissue Adhesive. Blood coagulation. Hemostasis. Platelet-rich plasma. Suture techniques.

Introduction

In situations involving tissue rupture, such as invasive surgical procedures or trauma, the most common method to restore hemostasis is traditional suture (Fapemig, 2013). Suture is defined as techniques and materials used to tie blood vessels and tissues conducting the healing process (Barros et al., 2011). This approach has been used since 2000 b.C when wires and animal fibers were used as suturing method (Souza, 2011). The healing process is dependent on the type of wire employed and this material is classified according to its degradation by the organism, its origin, number of filaments, and diameter (Santos et al., 2009). However, despite the existence of various wires that improve scar aesthetics, this approach can elicit rejection problems by the tissue. Thus, as the organism interprets suturing material as a foreign body, associated health problems and more obvious scar tissues can occur (Sandrini, Junior & Escoda, 2007). Other factors that might influence the healing process are age, physical condition of the patient, nutritional state, and metabolic alterations. Thus, it is not possible to determine the exact time until complete healing because it varies from patient to patient (Barros et al., 2011).

Due to the problems associated to traditional suture and regarding advances in surgical techniques, the fibrin glue (FG) emerged as an alternative to improve hemostasis (Dusse et al., 2008; Pizzoni et al., 2007). Another option of hemoderived sealant is the platelet gel (PG), which is formed by platelet rich plasma (PRP) (concentrated platelets and growth factors obtained by blood centrifugation, allowing a high level of platelets able to leakage growth factors and mimic the physiological process of hemostasis) (Dusse et al., 2008).

Brazil is a country presenting a huge amount of surgical procedures, especially plastic surgery, where perfection in the healing process is even more desired. In 2004, in Brazil, 800 thousand plastic surgeries were performed (Fapemig, 2013). The evidence of benefits associated to hemoderived sealant raises the interest in using these approaches in ordinary surgeries. Recently, the industry Hemobras (Empresa Brasileira de Hemoderivados e Biotecnologia) produces and supplies FG to the Brazilian public health system (Hemobrás, 2013).

Considering the interest in hemoderived sealant, the present work aimed to review relevant aspects of utilization of human hemoderived surgical glue, highlighting the difference between sealants, their advantages and benefits.

Data processing

The research was performed in Scielo, Pubmed, and LILACS databases, with the keywords “fibrin glue”, “platelet gel”, “fibrin sealant”, “platelet rich plasma”, and their Portuguese equivalents. Only manuscripts published after 2009 were considered, given priority to human experimental/clinical studies. It was found 95 manuscripts: 80 was excluded (52 because they were in animal models and 30 due to their subject differ from the focus of the present manuscript). Thirteen human experimental/clinical studies were summarized on Tables 1 and 2. Review articles were used to support the discussion and in the contextualization of the topic.

Fibrin glue

The FG is a biological concentrated formed by plasma components and obtained through the mixture of a fraction rich in fibrinogen and thrombin concentrate. This mixture forms a fibrin clot in about 2-10 seconds, reproducing the final steps of blood coagulation to reach hemostasis (Burnouf et al., 2009; Neto, Oliveira & Caldas, 2002).

The FG can be obtained using plasma fibrinogen isolated by centrifugation from 20ml blood. After separation of erythrocytes, plasma, and leukocytes, the fraction located between plasma and erythrocytes, which is rich in platelets and leukocytes, is aspired. Thrombin is obtained through the activation of coagulation cascade by the addition of a calcium-containing saline solution. The superior fraction of plasma is used as fibrinogen source, and FG is finally obtained after thrombin addition in the moment of the surgery (Pizzoni et al., 2007). There are autologous and homologous FG. They differ in the source of blood components employed. When blood components are obtained from the same person who will use the glue, it is autologous FG and when blood components are from donors, it is homologous (Burnouf et al., 2009).

FG using bovine fibrinogen is also described, however, this preparation might contain bovine factor V as a contaminant and it is related to cross-reactions with human factor V, causing hemorrhage (Dusse et al., 2008). It is important to refer that homologous FG can be prepared in industrial scale using plasma from donors or blood banks. Thus, fibrinogen and thrombin are isolated and kept separated in order to be mixed in the moment of the surgery, both being marketed in the lyophilized or frozen forms (Burnouf et al., 2009).

Homologous FG has a high risk of virus contamination since it is obtained by blood from many donors. Thus, in the industrial scale, there are inactivating/removing steps in order to exterminate virus, such as pasteurization, use of steam and heat, and nanofiltration (Burnouf., 2009).

These approaches are efficient in removing virus with lipid envelopes, such as hepatitis B and C and HIV, however they failed against virus without lipid envelope such as hepatitis A (Burnouf., 2009). Thus, autologous FG completely ends the risk of infectious disease transmission (Pizzoni et al., 2007)

Clinical aspects of FG utilization

Due to its hemostatic, adhesive, and cicatrizing properties, the FG widespread in many surgical fields, such as thoracic, cardiovascular, reconstructive, ophthalmic, and dental surgeries (Dusse et al., 2008). It is also employed in tissue reconstruction, isolated or with other suture techniques, or in grafts fixation (Silva et al., 2010). Due to its compatibility with human tissues, necrosis risk is decreased. This substance also shows a high ability to be colonized by cells, being degraded within a short period of time (Burnouf et al., 2009).

Comercial potential of FG

Currently, United States and Europe lead consumption of FG, reaching 500L/year (Hemobrása, 2013). In Brazil, until recently, the glue was only purchased through importation, increasing the costs (1ml=R\$500-1000,00) and consequently limiting the use. In this context, Brazil use to import only 3L/year (Hemobrása, 2013). This situation motivated the Ministry of Health, through Hemobras, to create a laboratory in charge to produce FG.

Regarding clinical applications of FG, ophthalmic surgeries occupy a prominent position (Rubin et al., 2011; Ghanem et al., 2010) and better results are observed in lesions in vessels and nerves (Testini et al., 2010). Advantages and disadvantages of FG use in humans are found in Table 1.

Table 1. Studies involving the use of FG in humans.

Surgery	FG preparation	Advantages	Disadvantages	Reference
Primary pterygium (eye).	Comercial FG.	Reduction in surgical time, redness and discomfort in the FG group compared to suture group.	Similar recurrences between FG group and nylon monofilament suture group.	(Rubin et al., 2011)
Primary pterygium (eye).	Comercial FG.	Reduction of conjunctive recurrences in the FG group compared to suture group.	There were no differences in corneal recurrence rates between groups.	(Ghanem et al., 2010)
Inguinal hernia.	Comercial FG.	Morbidity was lower in the FG group compared to suture group. Absence of pain reports in FG group, in the contrary to what was observed in suture group.	There were no differences in surgical time, hospitalization period, and time to return to normal activities between groups.	(Testini et al., 2010)

Inguinal hernia.	Comercial FG.	Lower rated of complications such as seroma formation, hematoma, and pain in FG group when compared to suture group.	One patient presented infection in the FG group.	(Descottes & Bagol d'Arc, 2009)
------------------	---------------	--	--	---------------------------------

Total knee arthroplasty.	Comercial FG formed by two components: fibrinogen and human thrombin dissolved in calcium chloride. Tranexamic acid was added as fibrinogen stabilizator.	Lower blood loss, hematomas and reduced transfusion need in FG group when compared to control group (using only Di-deco dispositive connected to two drains, without FG).	Blood loss during surgery was similar in both group due to tourniquet. Fever in both groups.	(Sabatini et al., 2012)
--------------------------	---	---	--	-------------------------

Total knee arthroplasty.	Comercial FG.		After surgery, the femoral canal of all treated patients was closed with an autologous bone plug and it was not observed	(Skovgaard et al., 2013)
--------------------------	---------------	--	--	--------------------------

differences in blood loss, edema, and pain between CF and placebo (saline solution supplemented with gentamicin) groups.

Hip arthroplasty.	Comercial FG.	FG and tranexamic acid groups show lower blood loss when compared to control group.	Tranexamic acid was used intravenously, and then it was not possible to directly compare the results obtained with tranexamic acid and FG.	(McConnell et al., 2011)
-------------------	---------------	---	--	--------------------------

Regarding ophthalmic surgeries, it was observed an increase in the use of FG, namely in conjunctive closure, glaucoma, ocular surface reconstruction, among others (Rubin et al., 2011; Ghanem et al., 2010). In the study performed by Rubin *et al*, 2011 aiming to compare the efficacy of autologous conjunctive graft fixation in primary pterygium surgery, it was demonstrated that the mean surgical time was about 19.05 ± 6.12 minutes in FG group and 48.5 ± 7.13 minutes in suture group, evidencing that FG significantly reduced the surgical time (Rubin et al., 2011). Ocular hyperemia was also lower in the FG group throughout postoperative period, probably due to the lower manipulation during surgery related to the reduced surgical time, the absence of a foreign body exposition, namely wire, and hemostatic properties of FG (Rubin et al., 2011).

Concerning the rate of relapse and postoperative complications of autologous conjunctive transplant using FG or suture, it was observed that the rate of corneal recurrence was lower in the FG group (7,5%), however, the difference was not statistically significant when compared to suture group

(12,1%). Nevertheless, considering the rate of conjunctive recurrence was significantly reduced in FG group (3.8%) when compared to suture group (13.8%), highlighting another advantage of FG (Ghanem et al., 2010).

Considering that one of the main approach to prevent inguinal hernia recurrence is the use of a mesh fixed with clamps and suture, the FG emerged as a less traumatic and more efficient method to fix it. In fact, in such patients, FG seems to enhance the recovery of the patient (Testini et al., 2010; Descottes & Bagol d'Arc, 2009).

When the rapid establishment of hemostasis is required, namely in total knee arthroplasty, when it is often a considerable blood loss that justifies blood transfusion, the FG emerged as a good option to reduce blood loss. Consequently, it reduces patient morbidity, hospitalization period, and hospital costs (Sabatini et al., 2012). However, results in the literature about the efficacy of FG in preventing blood loss are not consensual in this type of surgery. Despite some good results, in the study performed by Skovgaard *et al*, 2013, it was not observed a significant difference in blood loss measured through the evaluation of the drainage content in the FG group compared to placebo (saline solution supplemented with gentamicin) (Skovgaard et al., 2013). This discrepancy might be related to the occurrence to reactive hyperemia after tourniquet release, demonstrating that other factors such as technical and surgical skills are also crucial to the result.

Platelet Rich Plasma

The PRP is an autogenous source of platelets and their growth factors which aids on healing. PRP consists in platelet concentration obtained through gradient density by centrifugation (Pereira, 2012). One important difference between FG and PRP is that PRP consists in a huge concentration of platelets and native concentration of fibrinogen, which makes some authors point that PRP will replace FG soon (Pereira, 2012; Abreu, 2009).

PRP is obtained through centrifugation of freshly collected blood, after erythrocyte sedimentation (cellular fraction) and plasma separation. Plasma composition differs in the abundance of platelets and growth factors, with greater availability of these elements in the fractions immediately above the cellular portion (Abreu, 2009). After centrifugation, this portion is transferred to other tube, consisting in the PRP with ideal conditions to release growth factors (Dusse et al., 2008). Then, a thrombin source and calcium solution are added to PRP aiming to activate the coagulation system and resulting in the platelet gel (Dusse et al., 2008). One advantage of this approach is that PRP can be prepared during the surgery, using the PRP from the same patient (autologous). It is important to refer that PRP has to be prepared in aseptic conditions to avoid contamination (Dusse et al., 2008).

Clinical aspects of platelet gel utilization

The utilization of platelet gel in medical field is growing, evidencing a good potential in the integration of some grafts as bone and skin, and to stimulate scar healing since platelet gel stimulates cells involved in tissue repair to migrate to the lesion region, promoting cell proliferation, collagen and connective tissue production (Porcelleni, 2009). Since the 90's, platelet gel has been used mainly in dental (implant dentistry) and surgical reconstruction (Dusse et al., 2008). In 1995 platelet gel was used for the first time in the dental medicine aiming to fix bone grafts in the alveolar region for future dental implants, periodontal and maxillofacial surgery (Dusse et al., 2008). The use of autologous blood is indicated to avoid the possibility of disease transmission. Being an autogenous preparation, there are no risk of rejection by the patient, preventing infections at the surgical site (Messora et al., 2009).

Limitations in the PRP obtaining protocols

In the current literature, there are many different protocols (manual and automatized) to isolate PRP. The main objective is to obtain a greater number of viable platelets in the lowest plasma volume (Vendramin et al., 2006). However, many aspects needs to be clarified and validated in the available protocols, namely the best platelet and growth factors concentration and the influence of erythrocyte and leukocyte contamination in the PRP, since it is known that these factors influence PRP quality (Pereira, 2012). It is important to mention that the qualitative composition is more important than the quantitative aspect since a considerable number of platelet with compromised viability is not effective considering that growth factors are essential to its successful action (Dusse et al., 2008).

PRP comercial costs

With the emergence of simpler protocols and the possibility to obtain PRP using conventional centrifuges, costs related to PRP preparation decreased about ten-fold (Vendramin et al., 2006). The differences in the protocols concern the number of cells, centrifugation speed and time, as evidenced in the table 2.

Table 2: Studies involving the use of PRP in humans.

Surge ry	PRP preparation	Advantages	Disadvantages	Reference
Tibial osteotomy type Pudu.	Using an automatized cell separator and a plateletpheresis kit.		The use of PRP associated with aspirated bone marrow as an autologous bone graft did not show any advantage regarding pain and hemorrhage.	(D'Elia et al., 2009)
Shoulder surgery (rotator router).	Using cell separator and plateletpheresis kit.	Patients using PRP presented significant functional improvement and no full rupture postoperative.	One patient presented complication (adhesive capsulitis). Three patients presented partial postoperative.	(Malavolta et al., 2012)
Skin grafts surgery.	After blood collection, two centrifugations were made (400g, 10 minutes and 800g, 10 minutes).	The use of PRP in chronic wounds improved the integration and evolution of skin grafts.		(Vendramin, Franco & Franco, 2010)

The excess of platelet poor plasma was removed and the tubes were shaken to disperse platelets and finished the PRP preparation.

Patellar tendinopathy.	Recover system (centrifuge able to separate the platelet rich fraction and leukocytes)	PRP group showed a significant improve of the pain and recovery of the tendon compared to the group treated with cortisone and/or surgery.	The pain was not totally eliminated in the PRP group.	(Gosens et al., 2012)
	The PRP was isolated and buffered with sodium bicarbonate 8.4%. Then, bupivacaine, HCl 0.5% and adrenaline were added.			

Plantar fasciitis. Total blood was collected and centrifuged. The platelet concentrated previously isolated was buffered. Patients treated with PRP presented improve of the pain when compared to the group using corticosteroids. PRP helped to reverse the degenerative process of plantar fasciitis and contributes to the better healing due to the presence of growth factors compared to the group using only corticosteroids. (Peerbooms et al., 2010)

Patellar tendinopathy. It was collected three portions of PRP containing about 6.5 ± 1.5 million platelets. The In patients who surgical approach failed and then used PRP, it was observed an enhanced function of the (Filardo et al., 2010)

first portion	knee, and,
was	consequently,
administered	improve life
and other two	quality and the
was kept to -	ability to
30°C. Before	practice sports.
administratio	The cicatrization
n, sodium	was better in the
chloride was	PRP group when
added in	compared to
order to	patients
activate	subjected only to
platelet.	physiotherapy.

The use of PRP are also emerging in bone and cartilage surgeries. As evidenced in the table 2, contradictories results are observed considering the advantages/disadvantages of PRP in this type of surgery. The contradiction might be related to the different approaches used to obtain PRP, since there are many methodologies, which result in different and frequently not standardized amounts of platelets (D'Elia et al., 2009). Although, in the majority of manuscripts referred in the table 2, authors does not present the platelet concentration.

The postoperative rupture of rotator router affects a large number of patient. One of the main causes for this inconvenient is disability healing between tendon and bone (Malavolta et al., 2012). Therefore, PRP has been considered a valuable strategy in order to improve cicatrization (Malavolta et al., 2012).

Regarding skin graft surgeries, it is known that local healing process is dependent on tissue quality. In this sense, the use of PRP is considered a good method since it can improve granulation tissue quality (Vendrami, Franco & Franco, 2010).

Muscle injuries are more common in athletes, in general resulting from the excessive tension among muscle fibers that happen during running or jumping (Filardo et al., 2010). Currently, interventions such as surgeries and physiotherapy are performed aiming to repair these lesion, and it is known that sportive and orthopedic medicine has a strong interest in methods that minimize pain and disability, promoting a shorter recovery time of athletes (Filardo et al., 2010). In this context, PRP can be administered without surgery in order to promote tissue regeneration, enhancing scar

tissue aspect, reducing pain and hemorrhage (Gosens et al., 2010; Peerbooms et al., 2010; Filardo et al., 2010). In patients who do not respond to surgeries, the use of PRP as a treatment seems to be effective in increasing healing of the tendon in a less invasive way (Filardo et al., 2010).

Another advantage of PRP is the ability to regenerate degenerative processes such as plantar fasciitis, enhancing tissue regeneration through cytokines present in platelets, which increases the proliferation and migration of fibroblasts, vascularization and collagen deposition (Peerbooms et al., 2010). Although, despite some authors considered PRP as a promising alternative, the proof of its benefits is still needed (Gosens et al., 2012).

It is important to refer that there are confusing factors among some authors and physicians regarding the differences between PRP and FG. One limitation of the manuscripts selected is that, sometimes, detailed information about isolation protocols of hemoderived glues are absent.

Stability of FG and PRP

The preparation of FG involves the collection of superior plasma fraction in order to obtain fibrinogen. After processed, fibrinogen can be kept at -20°C for 2 years, being thawed and added to thrombin in the moment that FG is needed (Morais, Bizzacchi & Rossi, 1998).

In the study performed by Filardo *et al*, 2010, it was evidenced the stability of PRP in freezing temperatures since injections of PRP were kept at – 30°C for 1 month and they were still viable after thawed. Studies regarding longer storage time were not found in the literature.

Conclusion

Given the above discussed, it was evidenced that traditional suture has been gradually replaced by hemoderived sealant in the treatment of tissue trauma. These sealants, namely FG and PRP, present some benefits in comparison to other methods because they enhance the scar aesthetic, contribute for a better hemostasis, increase the regenerative ability of injured tissue, decrease time of cicatrization, and decrease risks related to infections and rejections.

The FG and PRP have been emerging in many medical field such as ophthalmic surgeries, dental interventions, bone and tissue reconstruction, in order to optimize healing process. Both substances are easy to obtain and present advantages for patients due to hemostatic properties and the ability to be degraded by the organism, decreasing necrosis risk. Currently, the utilization of FG is well established, being obtained by both autologous and homologous sources, or through commercial products. When possible, autologous sealants are preferred because it prevent the risk of disease transmission and rejection by the patient organism. PRP and platelet gel are promising alternatives to FG and some authors state that they will substitute FG due to its easy preparation and low cost of

production. The limitation evidenced by the present work concerning studies using PRP or platelet gel is to suppress important details of sealant preparation, namely centrifugation times and speed, standardization of viable platelets, which seems to be crucial to the success of the sealant.

In summary, in the present study, it was found that both human hemoderived glues are excellent surgical sealants, and it is expected that in the near future they replace other traditional suture techniques, evidencing a field with high potential for investments in the biomedical field.

Conflito de interesse:

Os autores declaram a inexistência de conflitos de interesses em relação ao presente artigo.

References

Abreu DC. *Análise quantitativa do número de plaquetas processadas no PRP*. 2009. Rio de Janeiro. 86 p. Monografia (Especialização em Implantes Dentários), Academia de Odontologia do Rio de Janeiro. Rio de Janeiro.

Barros M, Gorgal R, Machado AP, Correia A, Montenegro N. Princípios básicos em cirurgias: Fios de sutura. *Acta Med. Port.* 24(4): 1051-1056, 2011.

Burnouf T, Su CY, Radosevich M, Goubran H, Ekiaby M. Blood-derived biomaterials: fibrin sealant, platelet gel and platelet fibrin glue. *Journal compilation International Society of Blood Transfusion, ISBT Sci. Series.* 4(1): 136-142, 2009.

D'Elia CO, Rezende UM, Bitar AC, Tatsui N, Pécora JR, Camanho GL. O uso do plasma rico em plaquetas associado ao aspirado de medula óssea na osteotomia tibial tipo Puddu. *Rev. Bras. Ortop.* 44(6): 508-512, .2009.

Descottes B & Bagol d'Arc M. Fibrin sealant in inguinal hernioplasty an observational multicentre study in 1201 patients. *Hernia.* 13: 505-510, 2009.

Dusse LMSA, Macedo AP, Batschauer AP, Carvalho MG. Plasma Rico em Plaquetas (PRP) e sua aplicação em Odontologia. *Rev. Bras. Anál. Clín.* 40(3): 193-197, 2008.

FAPEMIG (Fundação de Amparo a Pesquisa do Estado de Minas Gerais). Cola Biodegradável para Sutura Cirúrgica. Disponível em: <<http://inventta.net/wp-content/uploads/2010/08/Cola-para-suturas.pdf>>. Acesso em: 20 abr. 2013.

Filardo G, Kon E, Villa KD, Vincentelli F, Fornasari PM, Marcacci M. Use of platelet-rich plasma for the treatment of refractory jumper's knee. *Intern. Orthopaedics.* 34:909-915, 2010.

Ghanem RC, Oliveira RF, Furlanetto E, Ghanem MA, Ghanem VC. Transplante autólogo de conjuntiva com uso de cola de fibrina em pterígios primários. *Arq. Bras. Oftalmol.* 73(4): 350-353, 2010.

Gosens T, Oudsten D, Fievez E, Spijker P, Fievez A. Pain and activity levels before and after platelet-rich plasma injection treatment of patellar tendinopathy: a prospective cohort study and the influence of previous treatments. *Intern. Orthopaedics.* 36:1941-1946, 2012.

HEMOBRÁS. Empresa Brasileira de Hemoderivados e Biotecnologia. Hospitais da rede pública do Estado do Rio de Janeiro passam a utilizar cola de fibrina, 2013. Disponível em: <<http://www.hemobras.gov.br/site/conteudo/noticia.asp?EditeCodigoDaPagina=13>>. Acesso em: 14 maio 2013.

HEMOBRÁS. Empresa Brasileira de Hemoderivados e Biotecnologia. Hospitais de Pernambuco recebem cola de fibrina. Secretaria Estadual de Saúde, 2013. Disponível em: <portal.saude.pe.gov.br/noticias/hospitais-de-pe-recebem-cola-de-fibrina-da-hemobras/>. Acesso em: 14 maio 2013.

Malavolta EA, Gracitelli MEC, Sundas EE, Benegas E, Prada FS, Bollinger Neto R, Rodrigues MB, Neto AAF, Camargo OP. Plasma rico em plaquetas no reparo artroscópico das roturas completas do manguito rotador. *Rev. Bras. Ortop.* 47(6): 741-747, 2012.

McConnell JS, Shewale S, Munro NA, Shah K, Deakin AH, Kinninmonth AWG. Reduction of blood loss in primary hip arthroplasty with tranexamic acid or fibrin spray. *Acta Orthop.* 82(6): 660-663, 2011.

Messora MR, Nagata MJH, Furlaneto FAC, Deliberador TM, Melo LGN, Garcia VG. Análise da eficiência do protocolo de dupla centrifugação para o preparo do plasma rico em plaquetas (PRP) estudo experimental em coelhos. *Rev. Sul-Brasileira de Odontol.* 6(3): 291-296, 2009.

Morais AM, Bizzacchi JMA, Rossi ABR. Use of autologous fibrin glue in dermatologic surgery: application of skin graft and second intention healing. *Rev. Paulista Med.* 116(4): 1747-1752, 1998.

Neto SC, Oliveira RL, Caldas N. Uso da colada de fibrina na prevenção de sangramento e hematoma pós-operatório em septoplastias. *Rev. Bras. Otorrinolaringol.* 68(5): 635-638, 2002.

Peerbooms JC, Laar WV, Faber F, Schuller HM, Hoeven HVD, Gosens T. Use of platelet rich plasma to treat plantar fasciitis: design of a multi centre randomized controlled trial. *BMC Musculoskelet Disord.* 11(69): 1-5, 2010.

Pereira RCF. *Avaliação de sete protocolos de obtenção de plasma rico em plaquetas (PRP)*. 2012. Santa Maria. 54 p. Tese (Mestrado em Medicina Veterinária), Universidade Federal de Santa Maria. Santa Maria.

Pizzoni VRSV, Franciosi LFN, Mueller SF, Fetter PR, Silveira L, Castan R. O uso da Cola de Fibrina autóloga como método de fixação de enxertos de pele. *Arq. Cat. Med.* 36(1): 183-185, 2007.

Porcellini A. Regenerative medicine: a review. *Rev. Bras. Hematol. Hemoter.* 31(2): 63-66, 2009.

Rubin MR, Dantas PEC, Dantas MCN, Felberg S. Eficácia do adesivo tecidual de fibrina na fixação de enxerto conjuntival autógeno em cirurgias de pterígio primário. *Arq. Bras. Oftalmol.* 74(2): 123-126, 2011.

Sabatini L, Trecci A, Imarisio D, Uslenghi MD, Bianco G, Scagnelli R. Fibrin tissue adhesive reduces postoperative blood loss in total knee arthroplasty. *J. Orthop. Traumatol.* 13:145-151, 2012.

Sandrini FAL, Pereira-Junior ED, Escoda CG. Anastomose do nervo facial de coelhos com cola de fibrina: estudo da velocidade de condução nervosa *Rev. Bras. Otorrinolaringol.* 73(2): 196-201, 2007.

Santos TO, Paes CA, Pereira DM, Gonçalves LGD. Fios de Sutura Absorvíveis. *Rev. Cient. Eletr. Med. Vet.* 7(2): 1-6, 2007.

Silva DN, Coelho J, Frazílio FO, Odashiro AN, Carvalho PTC, Pontes ER, Vargas AF, Rosseto M, Silva AB. End-to-side nerve repair using fibrin glue in rats. *Acta Cir. Bras.* 25(2): 158-162, 2007.

Skovgaard C, Holm B, Troelsen A, Lunn TH, Larsen LG, Kehlet H. No effect of fibrin sealant on drain output or functional recovery following simultaneous bilateral total knee arthroplasty. *Acta Orthopaedica.* 84(2): 153-158, 2013.

Souza MS. *Suturas na Implantodontia*. 2011. Rio de Janeiro. 129 p. Monografia (Especialização em Odontologia), Centro de Pós-graduação da Academia de Odontologia do Rio de Janeiro. Rio de Janeiro.

Testini M, Lissidini G, Poli E, Gurrado A, Lardo D, Piccinni G. A single-surgeon randomized trial comparing sutures, *N*-butyl-2-cyanoacrylate and human fibrin glue for mesh fixation during primary inguinal hernia repair. *Can. J. Surg.* 53(3):155-160, 2010.

Vendramin FS, Franco D, Franco TR. Utilização do plasma rico em plaquetas autólogo nas cirurgias de enxertos cutâneos em feridas crônicas. *Rev. Bras. Cir. Plást.* 25(4): 589-594, 2010.

Vendramin SF, Franco D, Nogueira CM, Pereira MS, Franco TR. Plasma rico em plaquetas e fatores de crescimento: técnica de preparo e utilização em cirurgia plástica. *Rev. Bras. Cir.* 33(1): 24-28, 2006.