DISERTASI

PENGARUH PEMBERIAN *PLATELET RICH FIBRIN* UNTUK MENCEGAH PEMBENTUKAN STRIKTUR ESOFAGUS AKIBAT CEDERA KAUSTIK BASA PADA HEWAN COBA TIKUS: TINJAUAN TERHADAP EKSPRESI Mmp1, Mmp8, Timp1

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UNIVERSITAS SRIWIJAYA

2024

HALAMAN PENGESAHAN

PENGARUH PEMBERIAN PLATELET RICH FIBRIN UNTUK MENCEGAH PEMBENTUKAN STRIKTUR ESOFAGUS AKIBAT CEDERA KAUSTIK BASA PADA HEWAN COBA TIKUS: TINJAUAN TERHADAP EKSPRESI Mmp1, Mmp8, Timp1

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***Lingkari salah satu jawaban, tempat anda melakukan pengecekan Similarity**

KATA PENGANTAR

Puji Syukur kepada Tuhan yang Maha Kuasa sehingga disertasi berjudul "**PENGARUH PEMBERIAN *PLATELET RICH FIBRIN* UNTUK MENCEGAH PEMBENTUKAN STRIKTUR ESOFAGUS AKIBAT CEDERA KAUSTIK BASA PADA HEWAN COBA TIKUS: TINJAUAN TERHADAP EKSPRESI Mmp1, Mmp8, Timp1**" dapat diselesaikan. Disertasi ini disusun untuk melengkapi salah satu syarat guna memperoleh gelar doktor pada Program Studi Sains Biomedis Program Doktor di Fakultas Kedokteran Universitas Sriwijaya.

Terlepas dari berbagai kendala yang dialami Penulis selama penulisan, disertasi ini dapat diselesaikan secara tepat waktu dengan hasil yang memuaskan. Penulis ingin menyampaikan ucapan terima kasih kepada berbagai pihak yang telah mendukung tercapainya penelitian dengan hasil yang memuaskan.

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Peneliti berharap bahwa disertasi ini dapat memberikan sekelumit sumbangsih untuk pengembangan ilmu pengetahuan. Akhirnya, Peneliti sangat mengharapkan saran dan kritik yang mendukung perbaikan di masa mendatang.

Palembang, Desember 2024

Puspa Zuleika

ABSTRAK

PENGARUH PEMBERIAN *PLATELET RICH FIBRIN* UNTUK MENCEGAH PEMBENTUKAN STRIKTUR ESOFAGUS AKIBAT CEDERA KAUSTIK BASA PADA HEWAN COBA TIKUS: TINJAUAN TERHADAP EKSPRESI Mmp1, Mmp8, Timp1

Cedera kaustik pada esofagus dapat menyebabkan striktur esofagus. Dalam penelitian lain, Mmp1, Mmp8, dan Timp1 berperan dalam patofisiologi striktur esofagus. Sejauh ini berbagai terapi telah diteliti untuk mencegah striktur esofagus dengan hasil dan biaya yang bervariasi. *Platelet-rich fibrin* telah digunakan secara aman dan efektif untuk meningkatkan regenerasi jaringan. Penelitian ini bertujuan untuk membuktikan peran PRF dalam mencegah pembentukan striktur esofagus pada model tikus. Penelitian ini dilakukan dalam dua tahap: validasi model striktur pada tikus secara non-invasif yang dipaparkan dengan NaOH 10% sebanyak 0,1 mL menggunakan sonde dan melihat dampak pemberian PRF pada volume 0,1 mL hingga 0,3 mL terhadap pembentukan striktur pada model tikus yang telah divalidasi sebelumnya. Pemberian PRF untuk tikus berasal dari tikus yang secara khusus disiapkan sebagai donor. Perbedaan ekspresi Mmp1, Mmp8, dan Timp1 diukur antara satu hingga empat belas hari melalui imunohistokimia sementara kerusakan jaringan dan *Stenosis Index* dinilai secara histologis. Penelitian ini berhasil memvalidasi model tikus yang dibuat. Penelitian ini telah menemukan bahwa PRF berpengaruh terhadap ekspresi Mmp1 dan Timp1 tetapi tidak berpengaruh terhadap Mmp8. Penelitian ini juga menemukan bahwa PRF menurunkan kerusakan jaringan dan *Stenosis Index* yang dinilai secara histologis. Striktur esofagus dalam penelitian ini dipengaruhi oleh hari perlakuan, volume PRF yang diberikan, ekspresi Mmp1 dan Timp1, serta kerusakan jaringan yang terjadi. Volume PRF terbaik untuk mencegah striktur ada pada volume 0,3 mL atau volume maksimal.

Kata kunci: *platelet-rich fibrin*, striktur esofagus, Mmp1, Mmp8, Timp1, model tikus

ABSTRACT

ELUCIDATING PLATELET-RICH FIBRIN'S ROLE IN PREVENTION OF CAUSTIC INJURY-RELATED ESOPHAGEAL STRICTURE OF RAT MODEL: EVALUATING CHANGES OF Mmp1, Mmp8, Timp1 EXPRESSION

Caustic esophageal injury may result in esophageal stricture. In other studies, Mmp1, Mmp8, and Timp1 are related to the pathophysiogical changes observed in esophageal stricture. Several prospective treatments to prevent esophageal stricture have been studied with varying costs and results. Platelet-rich fibrin has been proven to be safe and efficacious to improve tissue regeneration. This study aims to prove PRF's role in esophageal stricture prevention in the rat model. This study was divided into two phases: validation of a non-invasive rat model exposed to 0.1 mL of 10% NaOH via feeding tube and elucidation of the effect of varying volumes (0.1-0.3 mL) of administered PRF to prevent esophageal stricture on the previously-validated rat model. Platelet-rich fibrin originated from allograft rat donors. Differential expressions of Mmp1, Mmp8, and Timp1 were measured between 1-14 days through standardized immunohistochemical protocols while tissue damage and Stenosis Index were evaluated histologically. This study was able to validate the rat model. Further, this study discovered differential Mmp1 and Timp1 expression after administration while simultaneously discovering a non-significant impact of PRF administration on Mmp8 expression. This study also discovered reduction of histological tissue damage and Stenosis Index after PRF administration. This study discovered the differential role of time, PRF volume administered, Mmp1 and Timp1 expression, and tissue damage in stricture formation. This study discovered that stricture prevention is most significant when PRF was administered at maximum volume (0.3 mL).

Keywords: *platelet-rich fibrin, esophageal stricture, Mmp1, Mmp8, Timp1, rat model*

RINGKASAN

PENGARUH PEMBERIAN *PLATELET RICH FIBRIN* UNTUK MENCEGAH PEMBENTUKAN STRIKTUR ESOFAGUS AKIBAT CEDERA KAUSTIK BASA PADA HEWAN COBA TIKUS: TINJAUAN TERHADAP EKSPRESI Mmp1, Mmp8, Timp1

Karya tulis ilmiah berupa Disertasi, Desember 2024

Puspa Zuleika, dibimbing oleh Prof. Dr. dr. Mgs. Irsan Saleh, M.Biomed.; Prof. dr. Krisna Murti, Sp.PA, Subsp.HLE(K), M.Biotech.Stud., Ph.D.; dan Dr. Iche Andriyani Liberty, S.K.M., M.Kes.

Program Studi Sains Biomedis Program Doktor, Fakultas Kedokteran Universitas Sriwijaya

Xxi + 205 halaman, 25 tabel, 76 gambar, 10 lampiran

Striktur esofagus merupakan dampak jangka panjang yang mungkin terjadi dari cedera kaustik akibat basa kuat pasca cedera esofagus. Dalam berbagai penelitian yang telah dilaksanakan sebelumnya, diketahui bahwa Mmp1, Mmp8, dan Timp1 berperan dalam patofisiologi striktur esofagus. Sejauh ini berbagai terapi telah diteliti untuk mencegah striktur esofagus dengan hasil dan biaya yang bervariasi. Sebaliknya, *platelet-rich fibrin* telah digunakan secara aman dan efektif untuk meningkatkan regenerasi jaringan. Oleh karena itu, penelitian ini bertujuan untuk membuktikan peran PRF dalam mencegah pembentukan striktur esofagus pada model tikus.

Penelitian ini merupakan penelitian eksperimental *in vivo* dengan desain *post test-only controup group* yang dilakukan dalam dua tahap: validasi model striktur pada tikus secara non-invasif yang dipaparkan dengan NaOH 10% sebanyak 0,1 mL menggunakan sonde dan melihat dampak pemberian PRF pada volume 0,1 mL hingga 0,3 mL terhadap pembentukan striktur pada model tikus yang telah divalidasi sebelumnya. Pemberian PRF untuk tikus berasal dari tikus yang secara khusus disiapkan sebagai donor berdasarkan protokol yang telah disiapkan sebelumnya. Perbedaan ekspresi Mmp1, Mmp8, dan Timp1 diukur antara satu

hingga empat belas hari melalui imunohistokimia sementara kerusakan jaringan dan *Stenosis Index* dinilai secara histologis. Penelitian ini dilaksanakan di Laboratorium *Animal House* dan Laboratorium Bioteknologi Fakultas Kedokteran Universitas Sriwijaya serta Laboratorium Patologi Anatomi RSUP Dr. Mohammad Hoesin Palembang/Fakultas Kedokteran Universitas Sriwijaya antara bulan Januari hingga Juli 2024. Penelitian ini telah disetujui oleh Komite Etik Penelitian Kesehatan Fakultas Kedokteran Universitas Sriwijaya.

Penelitian ini berhasil memvalidasi model tikus non-invasif yang dibuat berdasarkan temuan kerusakan jaringan dan keberadaan *Stenosis Index*. Lebih lanjut, hasil analisis dari penelitian ini telah menemukan bahwa PRF berpengaruh terhadap ekspresi Mmp1 dan Timp1 tetapi tidak berpengaruh terhadap Mmp8. Penelitian ini juga menemukan bahwa PRF menurunkan kerusakan jaringan dan *Stenosis Index* yang dinilai secara histologis. Secara ringkas, dapat disimpulkan bahwa striktur esofagus dalam penelitian ini dipengaruhi oleh hari perlakuan, volume PRF yang diberikan, ekspresi Mmp1 dan Timp1, serta kerusakan jaringan yang terjadi. Volume PRF terbaik untuk mencegah striktur ada pada volume 0,3 mL atau volume maksimal.

Kata kunci: *platelet-rich fibrin*, striktur esofagus, Mmp1, Mmp8, Timp1, model tikus

SUMMARY

ELUCIDATING PLATELET-RICH FIBRIN'S ROLE IN PREVENTION OF CAUSTIC INJURY-RELATED ESOPHAGEAL STRICTURE OF RAT MODEL: EVALUATING CHANGES OF Mmp1, Mmp8, Timp1 EXPRESSION

Scientific paper in the form of Dissertation, December 2024

Puspa Zuleika, supervised by oleh Prof. Dr. dr. Mgs. Irsan Saleh, M.Biomed.; Prof. dr. Krisna Murti, Sp.PA, Subsp.HLE(K), M.Biotech.Stud., Ph.D.; dan Dr. Iche Andriyani Liberty, S.K.M., M.Kes.
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Xxi + 205 pages, 25 tables, 76 figures, 10 attachments

Esophageal stricture is one of the most dangerous late complication of caustic injury in esophagus. Several studies have mentioned the roles of Mmp1, Mmp8, and Timp1 in the pathophysiological changes observed in esophageal stricture. Several prospective treatments to prevent esophageal stricture have been studied with varying costs and results. On the other hand, platelet-rich fibrin has been proven to be safe and efficacious to improve tissue regeneration. This study is thus aimed to prove PRF's role in esophageal stricture prevention in the rat model.

This study wac conducted as an in vivo *experimental study designed with post test-only controup group in two phases*: *validation of a non-invasive rat model exposed to 0.1 mL of 10% NaOH via feeding tube and elucidation of the effect of varying volumes (0.1-0.3 mL) of administered PRF to prevent esophageal stricture on the previously-validated rat model. Platelet-rich fibrin originated from allograft rat donors. Differential expressions of Mmp1, Mmp8, and Timp1 were measured between 1-14 days through standardized immunohistochemical protocols while tissue damage and Stenosis Index were evaluated histologically. This study was conducted in the Animal House and Biotechnology Laboratory, Faculty of Medicine, Sriwijaya University. In addition, this study also involved Pathological*

Anatomy Laboratory, Mohammad Hoesin General Hospital/Faculty of Medicine Sriwijaya University. This study was conducted between Januari and June, 2024. This study has been approved by the Ethical Research Committee, Faculty of Medicine, Sriwijaya University.

This study was able to validate the rat model. Further, this study discovered differential Mmp1 and Timp1 expression after administration while simultaneously discovering a non-significant impact of PRF administration on Mmp8 expression. This study also discovered reduction of histological tissue damage and Stenosis Index after PRF administration. Briefly, this study was able to discover the differential role of time, PRF volume administered, Mmp1 and Timp1 expression, and tissue damage in stricture formation. This study discovered that stricture prevention is most significant when PRF was administered at maximum volume (0.3 mL).

Keywords: *platelet-rich fibrin, esophageal stricture, Mmp1, Mmp8, Timp1, rat model*

HALAMAN PERSETUJUAN PUBLIKASI

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Memberikan izin kepada pihak Promotor/Ko-promotor dan Universitas Sriwijaya untuk mempublikasikan hasil penelitian saya untuk kepentingan akademik apabila dalam kurun waktu satu tahun tidak mempublikasikan karya penelitian saya. Dalam kondisi tersebut, saya setuju untuk menempatkan Promotor sebagai penulis korespondensi (*corresponding author*).

Demikian pernyataan ini saya buat dengan sadar dan tanpa ada paksaan dari pihak manapun.

Palembang, Desember 2024

Puspa Zuleika

DAFTAR ISI

DAFTAR TABEL

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DAFTAR GAMBAR

Nomor **Judul** **Halaman**

DAFTAR SINGKATAN

95%CI : 95% *confidence interval*
ABB : *anorganic bovine bone*
ABC : *alveolar blood clots*
ABH : *alveolar bone height*
ABW : *alveolar bone width*
ADMSC : *adipose-derived mesenchymal stem cell*
AgNP : nanopartikel perak
ALG : alginat
AMI : *acute myocardial infarction*
APC : *argon plasma coagulation*
A-PRF : *advanced*-PRF
ASC : *adipose-derived stem cell*
BAPN : *beta-aminoproprionitrile*
BCP : *biphasic calcium phosphate*
BD : *biodegradable*
$CaCl_2$: kalsium klorida
cDNA : *circular* DNA
CGF : *concentrated growth factors*
CI : *confidence interval*
CM : *collagen membrane*
C-PRF : *concentrated*-PRF
CRP : C-*reactive protein*
CSBC : *calcium-silicate based-cement*
CT : *computed tomography*
CT-scan : *computed tomography-scan*
CVC : *central venous catheter*
DAMPs : *damage-associated molecular patterns*
dB : desibel
dkk. : dan kawan-kawan
DMEM : *Dulbecco's Modified Eagle Medium*
DROOL : *drooling reluctance oropharynx other leukocytosis*
ECM : *extracelullar matrix*
EGF : *epidermal growth factor*
ELISA : *enzyme-linked immunosorbent assay*
EuropePMC : *European PubMed Central*
FDG : *fluoro-d-glucose*
FGF : *fibroblast growth factor*
GADPH : *glyceraldehyde 3-phosphate dehydrogenase*
GDNF : *glial cell line-derived neurotrophic factor*
GLP-2 : *glucagon-like peptide-2*
H&E : hematoksilin dan eosin
HA : *hyaluronic acid*
HCl : asam klorida
HDS : *histopathological damage score*

HES : hesperidin
HGF : *human gingival fibroblast*
HL : *hearing loss*
HR : *hazard rasio*
IFN : interferon
IGF : *insulin-like growth factor*
IHK : imunohistokimia
IL : interleukin
iNOS : *inducible nitric oxide synthase*
i-PRF : *injectable*-PRF
kgBB : kilogram berat badan
KOH : kalium hidroksida
LA : *lumen area*
LLLT : *low-level diode laser radiation therapy*
L-PRF : *leukocyte- and platelet-rich fibrin*
LPS : lipopolisakarida
LV : *left ventricle*
Ly-PRF : *lysate*-PRF
MAPK : *mitogen-activated protein kinase*
MAPKK : MAPK kinase
MAPKKK : MAPKK kinase
MCP : *monocyte chemoattractant protein*
MD : *mean difference*
MDVP : *multidimensional voice program*
MMC : mitomycin C
MMP : *matrix metalloproteinase*
MMPs : *matrix metalloproteinases*
MRI : *magnetic resonance imaging*
mRNA : *messenger ribonucleic acid*
MSC : *mesenchymal stem cell*
N.IX : nervus kranialis IX (nervus glosofaringeus)
N.X : nervus kranialis X (nervus vagus)
NaCl : natrium klorida
NADPH : *nicotinamide adenine dinucleotide phosphate*
NaOH : natrium hidroksida
NF-kB : *Nuclear factor kappa-light-chain-enhancer of activated B cells*
NGF : *nerve growth factor*
NPV : *negative predictive value*
PAMPs : *pathogen-associated molecular patterns*
PDGF : *platelet-derived growth factor*
PET : *positron emission tomography*
PEWS : *pediatric early warning system*
PGE2 : prostaglandin E2
pH : *power of hydrogen, potential of hydrogen*
PLG : *polylactic glicolic acid*
PPP : *platelet-poor plasma*

PPRF : *pure* PRF
PPV : *positive predictive value*
PRF : *platelet-rich fibrin*
PRFM : PRF *matrix*
PRFr : PRF *releasate*
PRGF : *platelet-rich growth factors*
PRISMA : *Preferred Reporting Items for Systematic reviews and Meta-Analyses*
PRP : *platelet-rich plasma*
RDW : *red cell distribution width*
RNA : *ribonucleic acid*
ROS : *reactive oxygen species*
RT-PCR : *reverse transcriptase-polymerase chain reaction*
RT-qPCR : *reverse transcriptase-quantitative polymerase chain reaction*
SD : Sprague-Dawley
SEMS : *self-expanding metal stent*
SEPS : *self-expanding plastic stent*
SI : *stenosis index*
TA : *total area*
TGF : *tumor growth factor*
TNF : *tumor necrosis factor*
TQ : *thymoquinone*
Treg : sel T regulator
TTS : *through-the-scope balloon*
TUNEL : *terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling*
VEGF : *vascular endothelial growth factor*
WBC : *white blood cell*

BAB I
PENDAHULUAN

1.1. Latar Belakang

Cedera kaustik pada esofagus adalah cedera esofagus yang diakibatkan oleh tertelannya zat kimia kaustik yang bersifat asam atau basa.[1] Zat kaustik yang paling sering menyebabkan cedera esofagus karena tertelan adalah basa kuat (pH ≤ 12) atau asam kuat (pH ≥ 2). Kerusakan jaringan akibat zat basa lebih berat karena proses saponifikasi yang terjadi bersifat tidak kedap air sehingga zat alkali dapat memenetrasi lebih dalam ke jaringan di bawahnya.[2]

American Association of Poison Control Centers (AAPCC) pada tahun 2013 menyatakan bahwa terdapat hampir 60 ribu kasus paparan zat kaustik, yang terdiri dari 48 ribu kasus akibat paparan zat pemutih dalam rumah (pH 9-11), 7.500 kasus akibat paparan zat asam, dan 4.000 kasus akibat paparan basa.[3] Sebanyak 48% kasus di antaranya terjadi pada anak berusia di bawah lima tahun dan 25% dari kasus anak disebabkan oleh zat kimia kaustik yang terdapat di dalam kosmetik, produk perawatan tubuh, atau cairan pembersih rumah tangga. Sebanyak 75% dari 1.173 kematian yang terjadi akibat cedera kaustik pada remaja dan dewasa terjadi akibat kesengajaan dan melibatkan ingesti zat kaustik yang terdapat dalam cairan pembersih rumah tangga dalam jumlah dan konsentrasi yang tinggi.[4,5]

Benign esophageal stricture adalah komplikasi dari fibrosis esofagus yang disebabkan oleh berbagai cedera esofagus, seperti *gastroesophageal reflux*, radioterapi, konsumsi zat korosif, esofagitis eosinofilik, dan reseksi esofagus parsial.[6,7] Fibrosis esofagus terjadi akibat inflamasi merangsang aktivasi miofibroblas dan produksi protein matriks ekstraseluler, termasuk kolagen, secara berlebih.[7] Miofibroblas, selain mengekspresikan protein otot polos juga bersifat kontraktil. Kontraksi sel-sel ini berkontribusi pada patogenesis penyakit dan kegagalan jaringan. Proses perbaikan menghasilkan deposisi substansial komponen matriks ekstraseluler saat jaringan normal tergantikan dengan jaringan parut

permanen. Oleh karena itu, mediator seluler utama fibrosis adalah transformasi fibroblas-miofibroblas dan disposisi komponen matriks ekstraseluler.[7,8]

Penelitian Koval dkk. (2018) menemukan bahwa proses penyembuhan luka bakar akibat zat kaustik asam secara signifikan dipengaruhi oleh Mmps dan Timps. Penelitian ini menyatakan bahwa Mmp1, Mmp2, Mmp3, Mmp8, Mmp9, dan Timp1 berpengaruh terhadap proses penyembuhan luka baik normal maupun patologis pada mukosa esofagus akibat zat kaustik asam.[9] Senyawa Mmp1 disintesis oleh fibroblas, kondrosit, makrofag, keratinosit, sel endotel dan osteoblas dan memiliki aktivitas yang signifikan pada lingkungan sekitar luka.[9,10] Protein Mmp8 berperan dalam fase awal degradasi matriks ekstraseluler karena Mmp8 menjadi enzim kunci dari tahap awal penghancuran matriks ekstraseluler.[11] Melihat proses yang terjadi selama proses penyembuhan jaringan, kesetimbangan antara Timp1, Mmp1, dan Mmp8 sangat dipengaruhi oleh inflamasi yang terjadi pada jaringan dan menjadi topik pembahasan yang masih belum banyak diteliti.

Pembentukan striktur adalah komplikasi lambat yang paling sering terjadi pada cedera kaustik esofagus dan dinilai dengan menggunakan skor klasifikasi Zargar $\geq$ 2A, konsentrasi senyawa basa yang tertelan, meningkatnya hitung jenis sel darah putih, serta menurunnya rasio protrombin.[12] Sebanyak 71% pasien dengan derajat cedera 2B akan mengalami striktur esofagus; pada pasien dengan derajat Zargar 3, hampir seluruhnya mengalami striktur esofagus.[13] Striktur esofagus akibat cedera kaustik dapat memberikan gejala disfagia dan rasa tertekan pada substernum yang diikuti dengan rasa mual dan muntah setelah makan, serta penurunan berat badan akibat asupan yang kurang. Kondisi ini dapat terjadi sejak minggu kelima sampai minggu keenam setelah tertelan zat kaustik.[14]

Berbagai penelitian telah dilakukan dalam bidang pencegahan striktur esofagus, melibatkan eritropoietin, asam retinoat, ibuprofen, vitamin E, aseetilsistein, *dimethyl sulfoxide*, dan lain-lain. Akan tetapi hingga saat ini protokol tetap untuk penatalaksanaan pencegahan striktur akibat cedera kaustik di esofagus masih belum ditetapkan. Beberapa hambatan yang terjadi dikarenakan sulitnya ketersediaan zat tersebut, toksisitas, biaya yang tinggi, dan keamanan yang masih diragukan. Choukroun dkk. (2001) memperkenalkan konsentrat trombosit yang

disebut *Platelet-Rich Fibrin* (PRF), dapat dibuat tanpa antikoagulan apapun, dan mengandung sejumlah besar sel imun.[15] Beberapa penelitian telah menyatakan PRF saat ini relevan dalam perbaikan jaringan dan beberapa komponen PRF berperan dalam penyembuhan luka dan memiliki kemungkinan untuk penerapan dalam pengobatan regeneratif.[16] Maka dari itu PRF yang kaya dengan *growth factor*, leukosit, sitokin/kemokin, serta memiliki sifat *autologous* dapat dipertimbangkan untuk digunakan sebagai zat atau agen untuk mencegah terjadinya striktur esofagus akibat cedera kaustik pada esofagus.

1.2. Rumusan Masalah

1. Bagaimana pembuatan model striktur basa kuat pada tikus tanpa melalui laparotomi?
2. Apakah pemberian PRF secara topikal pada lumen esofagus dapat mencegah pembentukan striktur esofagus akibat cedera kaustik basa pada hewan coba tikus melalui ekspresi protein Mmp1, Mmp8, dan Timp1?

1.3. Hipotesis Penelitian

Pemberian PRF dapat mencegah pembentukan striktur esofagus akibat cedera kaustik basa pada hewan coba tikus melalui ekspresi protein Mmp1, Mmp8, dan Timp1.

1.4. Tujuan Penelitian

1.4.1. Tujuan Penelitian Umum

1. Menentukan metode pembuatan model tikus yang paling sesuai untuk pembuatan striktur esofagus akibat cedera kaustik basa kuat.
2. Membuktikan pengaruh pemberian PRF untuk mencegah pembentukan striktur esofagus akibat cedera kaustik basa kuat pada hewan coba tikus melalui ekspresi Mmp1, Mmp8, dan Timp1.

1.4.2. Tujuan Penelitian Khusus

1. Membuat model esofagitis korosif akibat trauma senyawa kaustik basa kuat pada tikus menggunakan sonde.
2. Menganalisis derajat kerusakan esofagus tikus yang mendapat perlakuan cedera kaustik basa kuat secara histopatologi.
3. Menganalisis perubahan ekspresi Mmp1, Mmp8, dan Timp1 pada jaringan esofagus akibat cedera kaustik basa kuat pada jaringan esofagus tikus.
4. Menganalisis dampak pemberian PRF terhadap perubahan histologis jaringan esofagus tikus model cedera kaustik basa kuat selama proses penyembuhan jaringan esofagus.
5. Menganalisis dampak pemberian PRF terhadap perubahan ekspresi Mmp1, Mmp8, dan Timp1 pada jaringan esofagus tikus model cedera kaustik basa kuat selama proses penyembuhan jaringan esofagus.
6. Menganalisis dampak variasi volume PRF terhadap proses penyembuhan esofagus tikus model cedera kaustik basa kuat.
7. Menganalisis dampak variasi volume PRF terhadap pencegahan striktur esofagus pada tikus model cedera kaustik basa kuat.

1.5. Manfaat Penelitian

1.5.1. Manfaat Akademik

Secara akademis, penelitian ini diharapkan mampu menjelaskan mekanisme kerja PRF dalam mencegah striktur esofagus akibat cedera kaustik basa kuat.

1.5.2. Manfaat di Bidang Penelitian dan Pengembangan

Untuk pengembangan penelitian, model hewan yang dikembangkan dalam penelitian ini diharapkan dapat menjadi dasar untuk penelitian lebih lanjut mengenai mekanisme kerja PRF dalam pencegahan striktur esofagus akibat cedera kaustik basa kuat.

1.5.3. Manfaat Klinis

Secara klinis, penelitian ini diharapkan dapat menjadi dasar untuk pemanfaatan PRF dalam mencegah striktur esofagus akibat cedera kaustik basa kuat di RSUP Dr. Mohammad Hoesin secara khusus dan *center* lain secara umum.

1.6. Keterbaruan Penelitian

Potensi kebaruan penelitian adalah dalam metode pembuatan model tikus yang bersifat non-invasif untuk striktur esofagus akibat cedera kaustik basa kuat serta mekanisme kerja PRF dalam pencegahan striktur esofagus melalui efeknya terhadap ekspresi Mmp1, Mmp8, dan Timp1. Potensi ini muncul karena:

1. Model tikus untuk striktur esofagus akibat cedera kaustik basa kuat yang paling umum digunakan saat ini bersifat invasif melalui laparotomi.
2. Peneliti masih belum menemukan publikasi penelitian mengenai pencegahan striktur esofagus akibat cedera kaustik basa kuat dengan tatalaksana PRF dan volume PRF yang paling efektif untuk pencegahan striktur esofagus akibat cedera kaustik basa kuat
3. Peneliti masih belum menemukan publikasi penelitian yang menilai ekspresi protein Mmp1, Mmp8, dan Timp1 dengan menggunakan imunohistokimia, derajat kerusakan histopatologi dan *Stenosis Index* setelah pemberian PRF untuk pencegahan striktur esofagus akibat cedera kuat

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