PENGARUH DURASI ISKEMIA-REPERFUSI PADA *ACUTE KIDNEY INJURY* (AKI) TERHADAP GAMBARAN SELULER TUBULOINTERSTISIAL RENALIS, KADAR *CYSTATIN C* DAN *GLOMERULAR FILTRATION RATE* (GFR) PADA TIKUS WISTAR

Skripsi

Diajukan untuk memenuhi salah satu syarat guna memperoleh gelar
Sarjana Kedokteran (S.Ked)

Oleh:
Ahadi Aulia Rahman
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FAKULTAS KEDOKTERAN
UNIVERSITAS SRIWIJAYA

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HALAMAN PENGESAHAN

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Judul Naskah : Pengaruh Iskemia- Reperfusi terhadap Gambaran Seluler Tubulointerstisial Renalis, Kadar *Cystatin C* dan *Glomerular Filtration Rate* (GFR) Tikus Wistar
Effect of Ischemia-Reperfusion Acute on Tubulointerstitial Renal Appearance, Cystatin C Level and Glomerular Filtration Rate (GFR) in Wistar Rats

Penulis : Ahadi Aulia Rahman
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*Nama dan tanda tangan seluruh penulis

ABSTRAK

Pengaruh Durasi Iskemia- Reperfusi pada *Acute Kidney Injury* (AKI) terhadap Gambaran Seluler Tubulointerstisial Renalis, Kadar *Cystatin C* dan *Glomerular Filtration Rate* (GFR) pada Tikus Wistar

Ahadi Aulia Rahman, Januari 2019, 175 halaman
Fakultas Kedokteran Universitas Sriwijaya

Latar Belakang: *Acute Kidney Injury* (AKI) merupakan penurunan fungsi ginjal yang terjadi cepat. Penyebab AKI terbesar adalah iskemia/reperfusi yang memicu respon inflamasi dan menyebabkan kerusakan ginjal. Inflamasi merupakan respon proteksi dan perbaikan jaringan, namun dapat menyebabkan fibrosis yaitu jaringan normal digantikan oleh matriks ektraseluler seperti kolagen. Kerusakan yang terjadi pada bagian tubulointerstisial berpengaruh besar terhadap fungsi ginjal. Fungsi ginjal dapat diukur dengan GFR menggunakan *cystatin C.* Tujuan penelitian ini adalah untuk mengetahui pengaruh durasi iskemia-reperfusi AKI terhadap gambaran seluler tubulointerstisial, kadar *cystatin C* dan GFR pada tikus Wistar serta mengetahui korelasi antara gambaran seluler tubulointerstisial, kadar *cystatin C* dan GFR pada tikus Wistar.
Metode: Penelitian ini adalah penelitian eksperimental dengan desain penelitian *posttest only with control group.* Objek penelitian tikus Wistar berjumlah 30 ekor, penelitian dilakukan di *animal house* dan laboratorium biomolekuler Fakultas Kedokteran Universitas Sriwijaya. Gambaran seluler tubulointerstisial, kadar *cystatin C* dan GFR dinilai dengan persentase fraksi area kolagen, ELISA dan rumus Larsson.
Hasil: Durasi iskemia 30 menit dan reperfusi 14 hari 99,1% berpengaruh terhadap persentase fraksi area kolagen, durasi iskemia 120 menit dan reperfusi 14 hari 98,8% berpengaruh terhadap kadar *cystatin C* serta 99,5% berpengaruh terhadap GFR. Terdapat korelasi yang signifikan antara persentase fraksi area kolagen dan kadar *cystatin C* (p=0,0001, r=0,901), persentase fraksi area kolagen dan GFR (p=0,0001, r=-0,834), serta kadar *cystatin C* dan GFR (p=0,0001, r=-915).
Kesimpulan: Terdapat pengaruh antara durasi iskemia-reperfusi terhadap gambaran seluler tubulointerstisial, kadar *cystatin C* dan GFR pada tikus Wistar serta terdapat korelasi antara gambaran seluler tubulointerstisial, kadar *cystatin C* dan GFR pada tikus Wistar.
Kata Kunci: *AKI, Persentase Fraksi Area Kolagen, Cystatin C, GFR*

ABSTRACT

The Effect of Ischemia-Reperfusion Duration in Acute Kidney Injury (AKI) on Tubulointerstitial Renalis Appearance, Cystatin C Level and Glomerular Filtration Rate (GFR) in Wistar Rats

Ahadi Aulia Rahman, January 2019, 175 pages
Medical Faculty of Sriwijaya University

Background: *Acute Kidney Injury (AKI) is rapid decline in renal function. Most causes of AKI are ischemia/reperfusion which triggers an inflammatory response and causes renal injury. Inflammation is a protective response and tissue repair, but it can cause fibrosis, which is the normal tissue replaced by an extracellular matrix such as collagen. Damage that occurs in the tubulointerstitial part has a large effect on renal function. Renal function can be measured by GFR using cystatin C. Kidney function can be measured by GFR using cystatin C. The purpose of this study was to determine the effect of ischemia-reperfusion duration in AKI on tubulointerstitial cellular appearance, cystatin C levels and GFR in Wistar rats and find out the correlation between tubulointerstitial cellular appearance, cystatin C levels and GFR in Wistar Rats.*

Method: *This research is an experimental research using posttest only with a control group design. The object of research is 30 Wistar rats, the study was conducted in animal house and biomolecular laboratory of the Faculty of Medicine, Sriwijaya University. Tubulointerstitial cellular appearance, cystatin C levels and GFR were assessed by percentage of collagen area fraction, ELISA and Larsson formula.*

Result: *The duration of 30 minutes ischemia and reperfusion 14 days 99.1% affected the percentage of the collagen area fraction, the duration of 120 minutes ischemia and 14 days reperfusion 98.8% influenced the levels of cystatin C and 99.5% influenced GFR. There was a significant correlation between the percentage of collagen area fraction and cystatin C levels ($p = 0,0001$, $r = 0,901$), percentage of collagen and GFR area fractions ($p = 0,0001$, $r = -0,834$), and cystatin C levels and GFR ($p = 0,0001$, $r = -915$).*

Conclusion*: There is effect between the duration of ischemia/reperfusion on tubulointerstitial cellular appearance, cystatin C levels and GFR in Wistar rats and there is correlation between tubulointerstitial cellular appearance, cystatin C levels and GFR in Wistar rats.*

Keyword: *AKI, Collagen, Cystatin C, GFR*

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Alhamdulillahirabbil'alamin, puji dan syukur kepada Allah SWT atas nikmat kesehatan dan kesempatan yang diberikan sehingga skripsi yang berjudul "**Pengaruh Durasi Iskemia- Reperfusi pada *Acute Kidney Injury* (AKI) terhadap Gambaran Seluler Tubulointerstisial Renalis, Kadar *Cystatin C* dan *Glomerular Filtration Rate* (GFR) pada Tikus Wistar**" ini dapat diselesaikan dengan baik dan tepat waktu. Skripsi ini disusun sebagai syarat untuk memperoleh gelar Sarjana Kedokteran (S.Ked) di Program Studi Pendidikan Dokter Umum Fakultas Kedokteran Universitas Sriwijaya.

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Palembang, 3 Januari 2019
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DAFTAR SINGKATAN

AKI	: *Acute Kidney Injury*
ATP	: *Adenine Tri Phosphate*
BCL-2	: *B Cell Lymphoma-2*
BIR	: *Bilateral Ischemia Reperfusion*
BMSCs	: *Bone Marrow Stromal Cells*
BUN	: *Blood Urea Nitrogen*
CCR2	: *C-C Chemokine Receptor Type- 2*
CD154	: *Cluster of Differentiation* 154
CD28	: *Cluster of Differentiation* 28
$CD4^+$	: *Cluster of Differentiation* 4 Plus
CD40	: *Cluster of Differentiation* 40
CKD	: *Chronic Kidney Disease*
Crry	: *Complement Regulatory Protein*
CTGF	: *Connective Tissue Growth Factor*
CX3CR1	: *CX3C Chemokine Receptor-1*
DCs	: *Dendritic Cells*
DNA	: *Deoxyribonucleic Acid*
ECM	: *Extra Cellular Matrix*
ELISA	: *Enzyme Linked Immunosorbent Assay*
EMT	: *Epithelial-Mesenchymal Transition*
ENA-78	: *Epithelial Neutrophil Activating Protein-78*
ERK	: *Extracellular Regulated Kinase*
ESRD	: *End Stage Renal Disease*
G2/M	: *Growth 2/ Mitosis*
GFR	: *Glomerular Filtration Rate*
GTPase	: *Guanosine Triphosphate*
HGF	: *Hepatic Growth Factor*
HSCs	: *Hematopoietic Stem Cells*
ICAM-1	: *Intercellular Adhesion Molecule-1*
ICU	: *Intensive Care Unite*
IFN-γ	: *Interferon Gamma*
IL-10	: *Interleukin- 10*
IL-12	: *Interleukin- 12*
IL-13	: *Interleukin- 13*
IL-15	: *Interleukin- 15*
IL-17	: *Interleukin- 17*
IL-18	: *Interleukin- 18*
IL-1β	: *Interleukin- 1 Beta*
IL-32	: *Interleukin- 32*
IL- 4	: *Interleukin- 4*
IL- 6	: *Interleukin- 6*
IL- 8	: *Interleukin- 8*
IR	: *Ischemia- Reperfusion*
IRI	: *Ischemia Reperfusion Injury*

ISM	: Iskemia
JNK	: *C-Jun N-Terminal Kinase*
KDIGO	: *Kidney Disease Improving Global Outcome*
KIM-1	: *Kidney Injury Molecule–1*
LMIR5	: *Leukocyte Mono-Ig-Like Receptor 5*
MAC	: *Membrane Attack Complex*
MAPK	: *Mitogen Activated Protein Kinase*
MCP-1	: *Monocyte Chemoattractant Protein- 1*
MHC II	: *Major Histocompatibility Complex*
MTAL	: *Medullary Thick Ascending Limb*
NCAM	: *Neural Cell Adhesion Molecule*
NGAL	: *Neutrophil Gelatinase-Associated Lipocalin*
NKT	: *Natural Killer T*
PPRRs	: *Prototypic Pattern Recognition Receptors*
$Rag1^{-/-}$	: *Recombination Activating Gen 1*
RANTES	: *Regulated Upon Activation Normal T Cell Express Sequence*
RASAL1	: *RAS Protein Activating Like-1*
RBF	: *Renal Blood Flow*
RNA	: *Ribonucleic Acid*
ROCK	: *Rho-Associated Coiled-Coil-Forming Protein Kinase*
ROS	: *Reactive Oxygen Species*
RPF	: Reperfusi
SIGIRR	: *Single Ig IL-1–Related Receptor*
SO	: *Shamed Operated*
TCRαβ	: *T Cell Immune Reconstitution Alpha Beta*
TCRγδ	: *T Cell Immune Reconstitution Gamma Delta*
TGF-β	: *Tissue Growth Factor- Beta*
Th2	: *T helper 2*
THP	: *Tamm Horsfall Protein*
TIR8	: *Toll–IL-1 Receptor 8*
TLR 2	: *Toll Like Receptor 2*
TLR 4	: *Toll Like Receptor 4*
TLRs	: *Toll Like Receptors*
TNF-α	: *Tumor Necrosis Factor Alpha*
TRAF 6	: *Tumor Necrosis Factor Receptor Associated Factor 6*
UIR	: *Unilateral Ischemia Reperfusion*
UUO	: *Unilateral Ureter Obstruction*
VEGF	: *Vascular Endothelial Growth Factor*
αSMA	: *Alpha-Smooth Muscle Actin*

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BAB I
PENDAHULUAN

1.1 Latar Belakang

Menurut *National Institute of Diabetes and Digestive and Kidney Disease* (2016) penyakit ginjal adalah keadaan ginjal yang mengalami gangguan dan tidak bisa menyaring darah sesuai dengan fungsinya. Penyakit ginjal dibagi menjadi penyakit ginjal tanpa gangguan fungsi ginjal dan penyakit ginjal yang disertai gangguan fungsi ginjal yang dibagi menjadi akut dan kronis (Beech *et al.*, 2018).

Gangguan ginjal akut atau *Acute Kidney Injury* (AKI) merupakan suatu sindrom yang ditandai dengan penurunan fungsi ginjal dalam mengatur keseimbangan komposisi cairan dan elektrolit tubuh, serta eksresi produk sisa metabolisme, yang terjadi secara tiba-tiba dan cepat bisa dalam hitungan jam hingga hari (Melyda, 2017). Menurut Pernefri (Perhimpunan Nefrologi Indonesia) (2016) jumlah penderita gangguan ginjal akut di Indonesia pada tahun 2016 yakni sebanyak 8% dari seluruh pasien yang menjalani hemodialisis di Indonesia. Tejera *et al.*, (2017) mengungkapkan terdapat sekitar 50,1% pasien yang berada di ICU menderita AKI. Adeera *et al.*, (2017) juga mengungkapkan bahwa insiden AKI selalu meningkat selama 20 tahun terakhir.

Penyebab gangguan ginjal akut dapat dibagi menjadi prerenal, intrinsik renal dan pasca renal, namun sekitar 70% dari semua kasus gangguan ginjal akut disebabkan oleh penyebab pre renal yaitu adanya cedera iskemik/reperfusi sehingga terjadi penurunan volume darah vaskular atau penurunan tekanan darah arteri yang tergambar melalui penurunan GFR *(Glomerular Filtration Rate)* (Awdishu dan Wu, 2017). Kerusakan yang disebabkan oleh iskemik/reperfusi akan melibatkan proses dari sistem imun baik itu sistem imun bawaan maupun sistem imun adaptif. Respon inflamasi berperan penting dalam patofisiologi gangguan ginjal akut. Dengan adanya disfungsi endotel maka akan memicu terjadinya pelepasan mediator inflamasi oleh tubulus proksimal yang mengalami iskemik. Mediator inflamasi tersebut antara lain sitokin proinflamasi (TNF-α, IL-6, IL-1β, dan TGF-β) serta sitokin kemotaksis (*Monocyte Chemoattractant Protein*- 1 (MCP-1), IL-8, serta

RANTES) (Devarajan, 2006). Iskemia juga menyebabkan penurunan produksi ATP yang mengakibatkan sel mengalami apoptosis atau nekrosis terutama di glomerulus, tubulus dan interstisium (Makris dan Spanou, 2016). Kerusakan yang disebabkan oleh iskemik/reperfusi memiliki ciri berupa adanya gangguan dalam aliran darah (Lee *et al.*, 2012) dan kemudian dilanjutkan dengan terjadinya reperfusi atau kembalinya aliran darah serta kebanyakan manifestasi klinis atau timbul setelah terjadi kerusakan yang melibatkan intrinsik renal (Lechner dan Risbano, 2014). Menurut Eltzschig dan Eckle adanya reperfusi aliran darah dan reoksigenasi dapat menambah keparahan kerusakan jaringan akibat cedera iskemik serta memicu timbulnya respon inflamasi yang disebut sebagai cedera reperfusi (2011). Selain terjadi peningkatan aliran oksigen, terjadi juga peningkatan ROS *(Reactive Oxygen Species)* dan infiltrasi neutrofil sehingga memperparah terjadi kerusakan (Lee *et al.*, 2012)

Proses inflamasi merupakan respon proteksi dan perbaikan jaringan, namun proses perbaikan yang tidak sempurna pada intrinsik renal dapat menyebabkan fibrosis renal. Fibrosis renal terjadi ketika jaringan normal digantikan oleh matriks ektraseluler seperti kolagen. Fibrosis yang terjadi di tubulointerstisial menyebabkan penurunan fungsi ginjal akut dan merupakan faktor resiko terjadinya penyakit ginjal kronis (CKD) dan penyakit ginjal tahap akhir (ESRD) (Meng, Nikolic-paterson dan Lan, 2014). Hasil penelitian Basile *et al.*, (2018) melaporkan bahwa perbaikan fungsi ginjal yang tidak sempurna ditemukan pada sekitar 35-71% pasien yang pernah menderita AKI sehingga berpotensi berkembang menjadi CKD atau ESRD.

Belakangan ini banyak penelitian dikembangkan untuk mengetahui pengaruh adanya riwayat kerusakan ginjal pada AKI dan hubungannya dengan CKD serta ESRD (Dhaun dan Webb, 2013). Pengembangan model hewan percobaan untuk mengetahui patofisiologi AKI sangat penting seiring dengan pengembangan terapi baru yang lebih efisien untuk mencegah morbiditas yang ditimbulkan dari adanya riwayat kerusakan pada ginjal (Bruce *et al.*, 2000). Model hewan percobaan yang biasa digunakan adalah tikus model IRI *(Ischemia Reperfusion Injury)* untuk mengamati proses AKI. IRI dapat dibagi menjadi beberapa jenis diantaranya *cold ischemia* dan *warm ischemia*. *Warm ischemia* bisa dikelompokkan menjadi

Bilateral Ischemia Reperfusion (BIR) dan *Unilateral Ischemia Reperfusion* (UIR) (dengan atau tanpa nefrektomi). Namun, terdapat beberapa kendala dalam penggunaan IRI diantaranya tidak semua model IRI dapat digunakan untuk mengamati mekanisme terjadinya AKI serta belum terdapat model baku yang sesuai untuk menggambarkan kerusakan seperti yang terjadi pada ginjal manusia (Clef *et al.*, 2016).

Kerusakan yang terjadi pada bagian tubulointerstisial renalis terutama yang disebabkan oleh iskemik/reperfusi berpengaruh besar terhadap fungsi ginjal (Widiana, 2014). Menurut *Kidney Disease Improving Global Outcomes* (KDIGO) (2013) untuk mengetahui seberapa besar kerusakan jaringan yang terjadi diperlukan pemeriksaan patologi, sedangkan untuk mengetahui fungsi ginjal dapat dilakukan pengukuran GFR, pengukuran ini berdasarkan pada kadar kreatinin atau bisa menggunakan *cystatin C. Cystatin C* merupakan protein yang disintesis oleh semua sel berinti dan ditemukan diberbagai cairan tubuh manusia. *Cystatin C* difiltrasi bebas oleh glomerulus dan tidak disekresi, kemudian direabsorpsi tetapi mengalami katabolisme hampir lengkap oleh sel epitel tubulus proksimal ginjal, sehingga tidak ada yang kembali ke darah, dengan demikian kadarnya dalam darah menggambarkan *Glomerular Filtration Rate* (GFR) (Meinardaniawati, Effendi dan Rahayuningsih, 2013).

Cedera atau kerusakan iskemia/reperfusi merupakan penyebab terbanyak pada AKI, kerusakan yang tidak diperbaiki dengan sempurna akan membentuk fibrosis. Fibrosis merupakan faktor resiko dalam perkembangan CKD atau ESRD. Untuk mengetahui seberapa besar kerusakan jaringan ginjal pada AKI dapat digunakan model hewan percobaan IRI yakni dengan melakukan pemeriksaan tingkat seluler dan fungsi ginjal melalui pengukuran *Glomerular Filtration Rate* (GFR) serta kadar *cystatin C*. Oleh karena itu dilakukanlah penelitian untuk mengetahui pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis, kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.

1.2 Rumusan Masalah

Berdasarkan uraian latar belakang diatas rumusan masalah dalam penelitian ini adalah sebagai berikut:

1. Bagaimana pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis pada tikus Wistar?
2. Bagaimana pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap kadar *cystatin C* pada tikus Wistar?
3. Bagaimana pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap *Glomerular Filtration Rate* (GFR) pada tikus Wistar?
4. Apakah terdapat korelasi antara gambaran seluler tubulointerstisial renalis dan kadar *cystatin C* pada tikus Wistar?
5. Apakah terdapat korelasi antara gambaran seluler tubulointerstisial renalis dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar?
6. Apakah terdapat korelasi antara kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar?

1.3 Tujuan Penelitian

1.3.1 Tujuan Umum

Untuk mengetahui pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis, kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar serta mengetahui korelasi antara gambaran seluler tubulointerstisial renalis, kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.

1.3.2 Tujuan Khusus

Penelitian ini secara khusus memiliki tujuan antara lain:

1. Mengetahui pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis pada tikus Wistar.
2. Mengetahui pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap kadar *cystatin C* pada tikus Wistar.

3. Mengetahui pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap *Glomerular Filtration Rate* (GFR) pada tikus Wistar.
4. Mengetahui korelasi antara gambaran seluler tubulointerstisial renalis dan kadar *cystatin C* pada tikus Wistar.
5. Mengetahui korelasi antara gambaran seluler tubulointerstisial renalis dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.
6. Mengetahui korelasi antara kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.

1.4 Hipotesis

H0 : Tidak terdapat pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis, kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.

H1 : Terdapat pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis, kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.

1.5 Manfaat Penelitian

1.5.1 Manfaat Teoritis

1. Hasil penelitian dapat mendukung teori mengenai pengaruh durasi iskemia-reperfusi pada *Acute Kidney Injury* (AKI) terhadap gambaran seluler tubulointerstisial renalis, kadar *cystatin C* dan *Glomerular Filtration Rate* (GFR) pada tikus Wistar.
2. Hasil penelitian dapat dijadikan bahan rujukan untuk penelitian selanjutnya.
3. Mengembangkan model hewan percobaan yang sesuai untuk penelitian yang akan datang.

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