APLIKASI KOMBINASI SEL PUNCA ALOGENIK ASAL TALI PUSAT DAN SERAT PERANCAH DENGAN DIAMETER NANO PADA MODEL CEDERA MEDULA SPINALIS

Ringkasan Disertasi

Untuk memenuhi sebagian persyaratan mencapai derajat S-3

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ABSTRAK

Latar Belakang :

Cedera medula spinalis/*spinal cord injury* (SCI) menyebabkan gangguan fungsi motorik, sensoris, dan otonom. Pemulihan kondisi neurologis pasien pasca cedera masih menjadi sebuah tantangan. Salah satu hambatan terbesar proses penyembuhan medula spinalis adalah neuro-inflamasi serta *debris clearance* yang tidak efektif. Selain intervensi terapetik yang ada, dibutuhkan terobosan intervensi regeneratif yang dapat menggantikan jaringan saraf yang cedera.

Metode Penelitian :

Penelitian ini bertujuan mengetahui pengaruh aplikasi kombinasi sel punca mesenkimal alogenik asal tali pusat dan perancah komposit PVA/Kitosan pada cedera medula spinalis. Pada prosesnya terdapat 3 tahap; uji mekanis berupa uji gugus kimia FTIR, uji kekuatan perancah, uji observasi SEM; uji biologis berupa uji biodegradabilitas perancah, uji viabilitas seluler, dan uji proliferasi seluler; dan uji hewan yang melibatkan anjing (*Canis Lupus Familiaris*) sebagai model cedera tulang belakang. Pengujian dibagi menjadi 3 kelompok yaitu kontrol tanpa perlakuan, perlakuan satu dengan instrumentasi implant dan perlakuan dua kombinasi instrumentasi, perancah PVA/Kitosan dan sel punca. Evaluasi regenerasi medula spinalis dilakukan dengan pengamatan klinis dan uji histopatologis.

Hasil Penelitian :

Hasil penelitian ini menunjukkan perancah PVA/Kitosan memiliki aspek mekanis dan biologis yang baik. Pada uji mekanis proses *elektrospinning* menghasilkan serat perancah dengan gugus kimia PVA (1150 dan 1650 cm^{-1}) dan Kitosan (1152 cm^{-1}) pada pemeriksaan FTIR, ukuran serat nano struktur sesuai SEM dengan rentang 460.25 ± 26.84 nm dan kekuatan mekanis sesuai uji UTM dalam rentang 120- 190 N. Pada uji biologis didapatkan perancah nanostruktur memiliki kemampuan biodegradabilitas 60,48% yang didukung oleh hasil viabilitas seluler

Histopathological examination revealed decreased hemorrhage, inflammation, and astrogliosis indicated by GFAP, increased myelination by LFB, and higher number of neuron cells by NeuN.

Keywords : scaffold, stem cell, PVA/Chitosan

RINGKASAN

Pendahuluan

Cedera medula spinalis/*spinal cord injury* (SCI) adalah gangguan neurologis pada sistem motorik, sensoris, dan otonom di level di bawah dari tempat cedera. Secara epidemiologis terjadi sekitar 0.98 juta kasus baru cedera medula spinalis sedunia, dengan prevalensi total 27.04 juta kasus. Kurang dari 1% pasien yang mengalami cedera medula spinalis akan pulih secara sempurna pasca perawatan di rumah sakit.

Epidemiologi menunjukkan tren semakin meningkat pada usia produktif, menekankan kepentingan untuk mengembangkan program terapi dan rehabilitasi yang efektif untuk mengurangi beban nasional secara sosial dan finansial.

Selama beberapa dekade terakhir, pemulihan kondisi neurologis pasien setelah cedera tulang belakang masih menjadi sebuah tantangan. Salah satu hambatan terbesar dalam proses penyembuhan sistem saraf pusat pasca cedera medula spinalis adalah proses neuro-inflamasi serta *debris clearance* yang tidak efektif. Sistem imun tubuh akan berusaha membatasi proses inflamasi untuk melindungi jaringan sehat melalui proses *microglial bordering* pada sekitar lesi cedera, dan *glial scarring* pada lesi cedera tersebut. Namun, hal tersebut mengakibatkan penurunan kapabilitas regenerasi sistem saraf pusat akibat keberadaan *inhibitory growth factor* dan *glial scar*.

Proses regenerasi juga terganggu akibat keberadaan ruang kistik pasca cedera yang menghambat potensi untuk proses migrasi sel. Hal tersebut menekankan pentingnya aspek matriks ekstraseluler dalam mendukung proses penyembuhan pasca cedera medula spinalis. Sebagai pengganti jaringan ekstrseluler yang rusak, keberadaan konsep perancah hadir untuk menjadi jembatan regenerasi sel dalam membentuk jaringan.

Selain jaringan perancah, sel punca atau sel progenitor merupakan platform biologis dengan potensi untuk mendukung perbaikan medula spinalis. Aplikasi dari kombinasi antara sel punca alogenik asal tali pusat dan perancah medula spinalis

serat ukuran nano dapat membantu proses penyembuhan dengan memberikan dukungan mekanis dan biologis pada proses regenerasi medula spinalis pasca cedera.

Penelitian ini memiliki tujuan utama untuk Mengetahui pengaruh aplikasi kombinasi sel punca alogenik asal tali pusat (*umbilical cord-derived mesenchymal stem cells*, UC-MSCs) dan perancah komposit Polivinil Alkohol/Kitosan (PVA/CS) pada cedera medula spinalis di model hewan coba anjing.

Metode Penelitian

Penelitian secara umum dibagi menjadi 3 tahapan:

1. **Tahap 1** – **Karakterisasi mekanis**,
   a. Identifikasi gugus kimia relevan
   b. Pengujian kekuatan mekanis
   c. Analisis morfologi permukaan
2. **Tahap 2 – Properti Biologis**
   a. Uji biodegradabilitas
   b. Uji viabilitas seluler
   c. Uji proliferasi seluler.
3. **Tahap 3 – Uji Hewan**
   a. Evaluasi toksisitas
   b. Perbaikan motoris dan sensoris
   c. Pemeriksaan histopatologis

Variabel penelitian adalah sebagai berikut

1. Variabel independen:
   a. Instrumentasi implan
   b. Intervensi perancah PVA/ kitosan dengan sel punca alogenik asal tali pusat
2. Variabel dependen:

a. Derajat toksisitas dengan nilai laboratorium (angka Hb, Hct, Leukosit, Trombosit, SGOT, ALP, BUN, Kreatinin, Ureum)
b. Fungsi klinis motoris dengan menggunakan skoring cBBB dan fungsi klinis sensori dengan menilai reaksi rangsang panas dan dingin
c. Derajat perdarahan dan inflamasi jaringan medula spinalis dari evaluasi patologi anatomi dengan pewarnaan hematoxylin dan eosin
d. Derajat regenerasi jaringan medula spinalis dari evaluasi patologi anatomi dengan pewarnaan *luxol fast blue*, GFAP, dan NeuN

3. Variabel Kontrol:
   a. Volume perancah PVA/CS dari proses *elektrospinning*
   b. Volume sel puncal mesenkimal alogenik asal tali pusat
   c. Induksi kompresi medula spinalis dengan balon kateter forgati

Pada studi hewan, cedera medula spinalis diinduksi menggunakan metode kompresi balon dengan kateter Forgatti pada anjing (*Canis lupus familiaris*) yang kemudian dibagi menjadi 3 grup dengan 4 anjing per grup, yaitu grup kontrol/model cedera (CD), instrumentasi saja (IM), dan kombinasi instrumentasi dengan sel punca-perancah (SC). Observasi dilakukan selama 56 hari, kemudian euthanasia diberikan dan jaringan medula spinalis diambil untuk evaluasi histopatologis.

Skala numerik dianalissi menggunakan *one-way* ANOVA dan Bonferroni *post-hoc test*. Sementara itu, variabel ordinal dianalisis menggunakan Kruskal-Wallis dan Mann Whitney U *post hoc*. Distribusi normalitas dinilai dengan tes Saphiro-Wilk. Analisis statistic dilakukan dengan IBS SPSS Statistics 25.0 2017.

Hasil Penelitian

1. Tahap 1 – Karakterisasi mekanis

a. Identifikasi gugus kimia relevan

   Gugus utama CS (1152 cm^{-1}) dan PVA (1650 cm^{-1} dan 1150 cm^{-1}) dapat teridentifikasi pada perancah.

b. Pengujian kekuatan mekanis

Kekuatan mekanis perancah 6 mL adalah 159 N dengan kekuatan tarik 41,3 kPa, sementara perancah 8 mL memiliki kekuatan mekanis 191 N dan kekuatan tarik 49,6 kPa

c. Analisis morfologi permukaan

Perancah 6 mL memiliki ketebalan 171.00 ± 4.72 µm, diameter serat 424.67 ± 42.94 nm, dan porositas 21.01 ± 1.58. Sementara itu, volume 8 mL memiliki ketebalan 228.67 ± 6.01 µm, diameter serat 414.33 ± 19.09 nm, dan porositas 21.23 ± 433. Meskipun perancah 8 mL memiliki porositas tinggi, terdapat banyak sumbatan saat produksi sehingga homogenitas seratnya kurang baik.

2. Tahap 2 : Properti biologis

a. Uji Biodegradabilitas

Degradasi paruh waktu (>50%) PVA/CS setelah perendaman dengan UC-MSCs ditemukan pada hari 14 (hari 1=23,01%; hari 3=35,04%; hari 7=42,41%; hari 14=51,81%; hari 21=60,48%).

b. Uji Viabilitas

Perancah PVA/Kitosan aman bagi sel dengan rata-rata viabilitas sel mencapai 59,00 % - 91,48%

c. Uji Proliferasi

Hasil uji proliferasi menunjukkan perancah tipis (6mL) memiliki kemampuan untuk memfasilitasi proliferasi sel yang lebih baik jika dibandingkan dengan perancah tebal (8 mL).

3. Tahap 3 : Uji Hewan

a. Evaluasi toksisitas

Berkurangnya berat badan dan leukositosis ditemukan di semua subjek pasca intervensi. Namun, tidak ada parameter yang berubah secara signifikan dibandingkan dengan pre-intervensi yang mengkonfirmasi bahwa terapi PVA/CS+UC-MSCs bersifat non-toksik.

b. Perbaikan Motoris dan Sensoris

Meskipun semua grup menunjukkan perbaikan cBBB, tren perbaikan motoris lebih tinggi secara signifikan pada grup SC dibandingkan grup CD ($p = .012$) dan IM ($p = .037$). Tidak ada perbedaan signifikan dari fungsi sensoris ($p > 0.05$).

c. Pemeriksaan histopatologis

Terdapat perdarahan intralesi yang lebih sedikit secara signifikan pada grup SC dibandingkan grup CD ($p = 0.019$) dan IM ($p = 0.045$) dari pewarnaan HE. Sementara itu, LFB menunjukkan demyelinisasi intralesi yang lebih sedikit pada grup SC dibandingkan grup CD ($p_{anterior}=0.016$; $p_{lateral\text{-}1} = 0.012$; $p_{lateral\text{-}2} = 0.007$) dan IM ($p_{anterior}=0.020$; $p_{lateral\text{-}1} = 0.048$; $p_{lateral\text{-}2} = 0.027$). Pewarnaan GFAP dan NeuN tidak bisa dianalisis secara statistik karena kerusakan pada grup CD.

Analisis

Perbaikan fungsional dari medula spinalis membutuhkan terapi komprehensif untuk menargetkan keempat pilar dari *Diamond Concept*. Terapi sel punca dapat memberikan *cellular platform* dengan sitokin neuroinduktif apabila diberikan bersama dengan terapi operatif rutin yang mempertahankan integritas struktural medula spinalis. Terapi sel saja tidak cukup untuk mempertahankan lingkungan kondusif untuk sel bekerja, sehingga terapi kombinasi sel punca dengan perancah dapat menjembatani keempat aspek dari *Diamond Concept* untuk menghasilkan neuroregenerasi pada area target.

Berbagai macam jenis material telah diteliti untuk menciptakan perancah pada medula spinalis. Bahan perancah yang ideal sebaiknya terdiri dari material yang kuat dengan biokompatibilitas yang baik dengan jaringan sekitar. Hal ini dicapai dari penggunaan polimer PVA dengan bahan biologis Kitosan. Karakterisasi perancah dilakukan untuk memastikan perancah memiliki diameter nano untuk meningkatkan ratio luas permukaan-volume serta memberikan porositas yang cukup untuk difusi biomolekuler sekaligus menghambat infiltrasi sel inflamasi. Selain itu, gabungan PVA/CS juga memiliki property unik berupa

peningkatan kekuatan tarik dan stabilitas structural pada lingkungan cair, sehingga sesuai untuk implantasi intrakanal.

Perbaikan dari cedera medula spinalis yang berat masih susah dicapai dan beban penyakit masih tinggi, diindikasikan dari YLD (*Years Lived with Disability*) yang tidak berubah dari 1990 hingga 2019. Model binatang pada studi ini diberikan paralisis motor total untuk menggambarkan efek terapeutik terapi kombinasi pada pasien dengan cedera berat. Regenerasi saraf yang dicapai ditunjukkan dari perbaikan motoris dan pemeriksaan histopatologis setelah observasi selama 56 hari, di mana fase ini sudah melewati fase akut dan subakut dari patofisiologi cedera medula spinalis. Studi sebelumnya telah melaporkan hasil yang sama menggunakan bahan perancah yang berbeda. Namun, hasil pada penelitian ini juga menekankan pentingnya kombinasi terapi perancah-sel punca dengan terapi mekanis yang merupakan terapi rutin dari cedera medula spinalis.

Sel punca mesenkimal mempromosikan perbaikan saraf dengan efek immunomodulasi yang mengurangi mikroglia pro-inflamatori (M1) dan mengaktivasi fenotipe anti-inflamasi (M2) melalui sekresi IL-4 dan IL-13, sekaligus mengurangi TNF-α dan IL-6. Respon inflamasi pasca cedera medula spinalis ini yang berperan dalam memburuknya kerusakan setelah trauma awal. Pada studi ni, mekanisme terapi sel punca pada cedera adalah menciptakan lingkungan kondusif untuk pertumbuhan akson dan perbaikan fungsional, seperti yang ditunjukkan dari demyelinasi yang lebih sedikit pada hasil uji. Sementara itu, mekanisme kerja perancah adalah mengurangi pembentukan vakuola, jaringan, dan kavitasi untuk meningkatkan densitas sel saraf pada area cidera. Hal ini dicapai dengan menghambat pembentukan glia yang berujung pada jaringan parut. Meskipun awalnya pembentukan jaringan perut glia bersifat protektif pada fase akut cedera, jaringan ini menjadi penhambat utama dari neuroregenerasi di cedera medula spinalis.

Kesimpulan

Neuroregenerasi pada cedera medula spinalis dapat tercapai bila semua aspek *Diamond Concept* terpenuhi. Perancah PVA/CS dapat menjadi sistem *homing* untuk terapi seluler di cedera medula spinalis dengan properti mekanis dan biologis yang baik. Aplikasi terapi perancah PVA/CS+UC-MSCs terbukti menghasilkan perbaikan klinis dan histopatologis pada model cedera medula spinalis anjing yang mendukung penggunaannya di masa depan untuk uji klinis di manusia.

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