Pengaruh terapi heparin terhadap proses inflamasi pada sepsis berat suatu kajian terhadap peran faktor transkripsi dan sitokin proinflamasi = Impact of unfractionated heparin on inflammation in severe sepsis assesment on the role of transcriptional factors and proinflammatory cytokine

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Abstrak

Latar Belakang: Proses inflamasi dengan respons maladaptif merupakan mekanisme terjadinya disfungsi multiorgan dan kematian pada sepsis. Heparin merupakan sediaan yang digunakan secara luas untuk terapi gangguan koagulasi, secara in-vitro heparin juga memiliki pengaruh sebagai antiinflamasi melalui penurunan aktivitas nuclear factor kappa B (NFkB) dan tumor necrosis factor alpha (TNF-. Penggunan heparin pada sepsis, khususnya sebagai antiinflamasi, masih merupakan kontroversi dan memerlukan penelitian lebih lanjut.

Tujuan Penelitian: Tujuan primer penelitian ini adalah mengetahui pengaruh terapi heparin terhadap konsentrasi NFkB, inhibitor kappa B kinase beta (IKK dan TNF-pada pasien sepsis berat Tujuan sekunder adalah menilai pengaruh terapi heparin terhadap mortalitas dan perbaikan disfungsi organ.

Metode: Uji klinis acak tersamar ganda membandingkan terapi heparin tidak terfraksinasi, dosis 10 unit/kg berat badan/24 jam, infus kontinu selama 72 jam, dengan plasebo. Kriteria inklusi adalah: subjek usia 18 tahun atau lebih dengan sepsis berat awitan maksimal 48 jam dan bersedia berpartisipasi dalam penelitian. Seleksi subjek dilakukan secara konsekutif dengan alokasi subjek secara acak. Pemantauan terhadap respons klinis dilakukan dengan menilai mortalitas 14 hari serta perbaikan skor APACHE II. Analisis intention to treat (ITT) dilakukan terhadap subjek yang telah mendapat terapi heparin minimal selama 24 jam, pada subjek yang melengkapi seluruh protokol penelitian dilakukan analisis per-protocol (PP).

Hasil: Sebanyak 115 subjek telah diinklusi dan dirandomisasi, 58 subjek mendapat heparin dan 57 subjek plasebo. Rentang usia 21 hingga 82 tahun dengan rerata 51 tahun. Analisis ITT dan PP dilakukan terhadap masing-masing 46 dan 22 subjek kelompok heparin dan 50 dan 28 subjek kelompok kontrol. Tidak didapatkan perbedaan yang bermakna konsentrasi NFkBterfosforilasi dan IKK terfosforilasi kelompok heparin dibandingkan kontrol. Didapatkan penurunan konsentrasi TNF-pada kelompok heparin dibandingkan kontrol walaupun secara statistik belum bermakna. Didapatkan penurunan mortalitas pada analisis PP (RR 0,212 [IK 95% 0,053 - 0,815], p = 0,008), dengan ARR 33,8 % dan NNT 3. Terdapat kecenderungan perbaikan disfungsi organ pada kelompok heparin, walaupan secara statistik belum menunjukkan kemaknaan.

Simpulan: Terapi heparin memberikan pengaruh terhadap proses inflamasi pada pasien sepsis berat, terlihat dari penurunan konsentrasi TNF-, walaupun pada pengujian statistik tidak didapatkan perbedaan

bermakna. Tidak didapatkan pengaruh terapi heparin terhadap penurunan konsentrasi IKKdanNFkB. Heparin memberikan manfaat terhadap penurunan mortalitas, terutama pada subjek yang mendapat heparin selama 72 jam. Pada pengamatan selama 72 jam, heparin belum telihat memberikan pengaruh terhadap perbaikan disfungsi organ.
<hr>Background. Multiple organ dysfunction and mortality in sepsis are developed as the consequence of the inflammation with maladaptive host response. Heparin has been widely used as an anticoagulant treatment. Based on in vitro evaluation, heparin has an antiinflammatory property by reducing the activity of nuclear factor kappa B (NFkB) and tumor necrosis factor alpha (TNF-. However, the effect of heparin as the anti-inflammatory agent is still controversial. To ascertain the anti-inflammatory effects of heparin in sepsis, further study is needed.

Objectives. The primary aim of this study was to determine the effect of heparin in severe sepsis based on the concentration of NFkB, Inhibitor kappa B kinase beta (IKK), and TNF-. Secondary objective was to determine the effect of heparin on mortality rate and improvement of organ dysfunction.

Methods. A randomized, double-blind, clinical trial was conducted to compare the unfractionated heparin (UFH) treatment, in dosage of 10 units/ kg BW for 24 hours, continuous infusion for 72 hours, in comparison to placebo. The inclusion criteria were subject 18 years old or above, with severe sepsis in maximum 48 hours after onset and agreed to participate in this study. Furthermore, subjects were consecutively selected and randomly allocated. Clinical responses were monitored by evaluating the 14-days mortality rate and improvement of APACHE II score. Subjects who had received heparin treatment for at least 24 hours were analyzed by intention to treat (ITT), while others who had completed all the protocol, were analyzed by per protocol (PP).

Results. There were 115 subjects included and randomly assigned to heparin (n = 58) and placebo (n = 57) groups. The range of age was 21 to 82 years, mean of age was 51 years. ITT and PP analysis were conducted to 46 and 22 subjects in heparin group; 50 and 28 subjects in control group respectively. There were no significant differences in concentration of Phosphorylated-NFkB and Phosphorylated-IKK in both groups. The concentration of TNF-decreased in heparin groups, although statistically was not significant. The 14 days mortality rate reduced in PP analysis (RR 0.212 [95% CI 0.053 – 0.815], p = 0.008), with ARR 33.8 % and NNT 3. Moreover, there are trend of organ dysfunction improvement in heparin group, yet not statistically significant.

Conclusion. Heparin treatment has an impact on inflammatory process in severe septic patients; as shown in the reduction of the TNF- concentration, although was not significant statistically. There was no clear impact of heparin treatment on IKK and NFkB concentration. Moreover, heparin shows benefit in reducing the mortality, especially in subjects who has received heparin for 72 hours. No benefit on improvement of organ dysfunction was shown in 72-hour monitoring of heparin treatment.