THE ROLE OF INTENSIVE INSULIN THERAPY ON SUPEROXIDE DISMUTASE (SOD), TUMOR NECROSIS FACTOR-α (TNF-α), AND INTERLEUKIN-6 (IL-6) ON HYPERGLYCEMIA IN CRITICALLY ILL PATIENTS

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Abstract

Hyperglycemia and insulin resistance are common in critically ill patients in the ICU, although they have not previously had diabetes. It has been reported that pronounced hyperglycemia may lead to complications in such patients, and cause the reactive oxygen species (ROS) production, although controlled trial data are still lacking. The current debatable issue, focusing on whether the intensive insulin therapy, aimed at normalizing blood glucose, may improve patients'prognosis. Then, the debate is mainly about the time to start the therapy, and target of blood glucose level. Therefore, this research is mainly designed and aimed at knowing the difference between intensive insulin therapy and conventional insulin therapy on the increase of superoxide dismutase (SOD), decrease of cytokine production (TNF-α and IL-6), increase of albumin level, and event of SIRS

This study was carried out in a randomly pre and post-test control group design, involving 40 adult patients being nursed through the ICU Sanglah hospital Denpasar. They were randomly assigned to receive intensive insulin therapy, in which blood glucose was decreased and maintained at the level between 80-110 mg/dl, or conventional insulin therapy in which the insulin was infused only if the blood glucose level exceeded 215 mg/dl, decreased and maintained then at the level between 180-200 mg/dl.

The result of the study showed that there was (1) significant increase of SOD mean level (370. 70 vs 98.50 U/gHb, p=0.001); (2) no significant decrease of TNF-α mean level; (3) significant decrease of IL-6 mean level (10.26 vs 2.25; p=0.023); (4) significant increase of albumin mean level (0.62 vs 0.22); (5) significant decrease of SIRS (10 % vs 40 %, p=0.000) on intensive insulin therapy group compared to conventional insulin therapy group. It can be concluded that intensive insulin therapy could maintain blood glucose level between 80 – 110 mg/dl, increase SOD level, decrease IL-6 level, increase albumin level, and decrease SIRS on hyperglycemia in critically ill ICU patients.

Key words: *hyperglycemia, intensive insulin therapy, conventional insulin therapy, super oxide dismutase (SOD), critically ill patients, pro-inflammatory cytokine, albumin, and SIRS.*

Introduction

Critically ill patients being nursed through the ICU tend to have hyperglycemia, the so-called stress diabetes or newly diabetes, since such the anti-regulation hormones as epinephrine, nor-epinephrine, catecholamine, and glucagons are removed. Hyperglycemia may increase ROS through both enzymatic process, reaction of ox-phos and ADPH-oxide, and non-enzymatic process that generates gluco-oxidant and glycation. SOD is an enzyme that functions as anti-oxidant only if superoxide ion is produced in mitochondria. It has been known that there is a close relation between hyperglycemia and immune dysfunction, particularly infection. The ROS on hyperglycemia may activate transcription factor of NF-kB that stimulates the production of inflammatory cytokine, such as TNF-α and IL-1. With its otocrine and paratocrin effects, inflammatory cytokine may stimulate the other cytokine, IL-6. Therefore, the inflammatory cascade systemically happened. This may result in the decrease of albumin production in heart.

Insulin is considered to be the most rational anti-diabetes medicine recently because of its anabolic function. However, it is frequently assumed to lead serious complications like hyperglycemia. Besides, there is still a debatable issue about blood glucose level reached with insulin therapy.

Research Methodology

This research was an experimental study which was carried out in a randomly pre and post-test control group design on intensive insulin therapy group and conventional insulin therapy group.

Results and Discussion

Superoxide Dismutase (SOD) Level on Intensive Insulin Therapy Group and Conventional Insulin Therapy Group

The result of the study showed that mean level of SOD on the pre-test of intensive insulin therapy was 1,084.90 ± 193.43 U/gHb, and it was 1,049.40 ± 166.58 on the pre-test of conventional insulin therapy. On the Seventh day of the post-test on intensive insulin therapy, level of SOD was 1,455.60 ± 180.25 U/gHb, and it was 1,147.90 ± 165.42 U/gHb on the post-test of conventional insulin therapy. The result of the analysis of paired sample test showed that there was a significant increase on the mean level of SOD on the pre and post-test intensive insulin therapy to both groups (p=0.001). The result of the analysis of *t test* showed that there was a significant difference between the level of SOD on both the post-test intensive insulin therapy and conventional insulin therapy, in which p=0.001. Meanwhile, the increase of mean level of SOD (Δ SOD) on intensive insulin therapy group was 370.70 ± 163.35 U/gHb, and it was 98.50 ± 96.14 U/gHb on conventional insulin therapy group.

It can be then concluded that there was over production of superoxide ion on hyperglycemia. In order to reduce the negative effect of the oxidative stress, a huge number of SOD level must be needed. This may lead to the decrease of ROS level and reach normal level of SOD

TNF-α Level on Intensive Insulin Therapy Group and Conventional Insulin Therapy Group

The result of the study showed that level of TNF-α on the pre-test intensive insulin therapy group was 10.26 ± 7.22 pg/ml. Meanwhile, it was 8.15 ± 6.29 pg/ml on that of conventional insulin therapy group. On the Seventh day of the post-test, TNF-α on intensive insulin therapy group was 7.28 ± 2.77 pg/ml, meanwhile it was 8.78 ± 4.48 pg/ml on conventional insulin therapy group. On the basis of paired sample test, there was no significant difference on both intensive insulin therapy group (p=0.078) and conventional insulin therapy group (p=0.713). Furthermore, the result of *t* test on level of TNF-α on the post-test to the two groups showed that there was no significant decrease of level of TNF-α (p=0.211). Meanwhile, the result of *t* test on the mean level (Δ TNF-α) of TNF-α

showed that there was no significant difference among the two groups, either (2.98 vs. 0.63, p=0.977)

This might be caused by the difficulty of finding the appropriate time to detect the existence of TNF-α, the instability of TNF-α in blood, and such other risky factors as central obesity, alcohol consumption, and other uncontrollable genetic factors. Besides, TNF-α production was influenced by many factors, such as stress or disease causing hyperglycemia of which treatment had not been perfect yet.

IL-6 Level on Intensive Insulin Therapy Group and Conventional Insulin Therapy Group

The result of the study showed that level of IL-6 on the pre-test intensive insulin therapy group was 23.21 ± 9.63 pg/ml, and it was 20.35 ± 10.17 on conventional insulin therapy group. The result of Kolmogorov-Smirnov's normality test showed that the two groups were in normal distribution. The result of *t* test showed that there was no significant difference among the two groups (p=0.366). On the seventh day of the post-test, it was found that the post-test IL-6 level on intensive insulin therapy was 12.96 ± 7.81 pg/ml. In the meantime, the post-test IL-6 level on conventional insulin therapy group was 18.32 ± 7.11 pg/ml. The data also showed that there was a decrease of level of IL-6, either on intensive insulin therapy group or conventional insulin therapy group. On paired samples test, it was found that there was a significant decrease of level of IL-6 on intensive insulin therapy group (p=0.001), but not on conventional insulin therapy group (p=0.411). Then the result of the analysis of *t* test on the post-test IL-6 level showed that there was difference among the two groups. The *t* test result on the decrease of mean value of IL-6 level (Δ IL-6) on the two groups showed a significant difference (10.25 vs. 2.02; p=0.023)

The above analysis or study indicated different result due to the fact that on the conventional insulin therapy group blood glucose was maintained within hyperglycemia (80 – 110 mg/dl), while blood glucose on intensive insulin therapy was maintained to normal limit so that the production of oxidative stress on

conventional insulin therapy group was still higher than intensive insulin therapy group. Therefore, the production of inflammatory mediator was higher on conventional insulin therapy group.

Albumin level on Intensive Therapy Group and Conventional Insulin Therapy Group

Pre-test result of albumin level on intensive insulin therapy group was 2.75 ± 0.58 mg/dl, while it was 2.83 ± 0.43 on conventional insulin therapy group. The post-test result of albumin level on intensive insulin therapy group was 3.38 ± 0.40 mg/dl, while it was 3.06 ± 0.32 mg/dl. On the paired sample test, there was a significant increase on both intensive insulin therapy (p=0.001) and conventional insulin therapy (p=0.001). The result of T test analysis on level of albumin after the insulin therapy (post-test) on the two groups showed a significant difference (p=0.009). T test on the increase of mean albumin value (Δ Albumin) on the two groups showed that there was a significant difference among the two groups (0.62 vs. 0.22; p=0.001)

The different result was caused by such factors as hyperglycemia may improve permeability of blood vessel that makes the albumin move to the interstitial and forms *mikroalbuminuria*. Besides, hyperglycemia will increase the production of oxidative stress that may decrease the production of albumin in hearth.

The Event of SIRS on Intensive Insulin Therapy Group and Conventional Insulin therapy group

The result of the study showed that there were 2 people (10 %) who were in SIRS found on intensive insulin therapy group, while on conventional insulin therapy group; it was found 9 people (45 %). After having analyzed using Fisher's exact test, there was a significant decrease on the number of people who were in SIRS on the intensive insulin therapy group compared to conventional insulin therapy group (p=0.001). Besides, the result of the analysis also showed that the Odds ratio of the event of SIRS was 0.136 in which the trust interval was

0.025 – 0.748. Meanwhile, the relative risk to the event of SIRS on the two groups was 0.222 in which the trust interval was 0.055 – 0.902.

This event happened because on conventional insulin therapy group, blood glucose was maintained at the level of hyperglycemia. This may improve the production of reactive oxygen mixture as oxidative stress that may activate NF-kB and stimulate the production of pro-inflammatory cytokine, such as TNF-α, IL-1, and IL-6 Moreover, hyperglycemia may cause the decrease of fagositic function of fagosit cell.

Novelty

1. Intensive insulin therapy on hyperglycemia can regulate blood glucose quickly so that it can increase the production of anti-oxidant; decrease the production of IL-6, increase level of albumin, and decrease event of SIRS.
2. SOD enzyme as anti-oxidant increased higher after the infusion of intensive insulin therapy rather than conventional insulin therapy.

Conclusion

Intensive insulin therapy on hyperglycemia is better than conventional insulin therapy. It can decrease the production of ROS to a lower level. Therefore, level of SOD increases. It can decrease the production of inflammatory cytokine like IL-6 so that it can decrease the event of SIRS, improve permeability of blood vessel, reduce the divulgence of albumin, so that it improves patients' clinical outcome. Besides, there is no significant difference on complication of hyperglycemia by intensive insulin therapy.

Suggestion/Recommendation

1. Further research or study is needed with the same methodology in order to know the role of ROS on the production of other mediators, such as NO, ICAM, VICAM, and VEGF giving negative impact to endotil

2. Research variables should be sustainably checked in accordance with betterment of disease, so that the accurate data of clinical output, regarding cause and effect relation of those variables, can be acquired.

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PERANAN TERAPI INSULIN INTENSIF TERHADAP *SUPER OXIDE DISMUTASE*, *TUMOR NECROSIS FACTOR - α* DAN *INTERLEUKIN - 6* PADA PENDERITA KRITIS DENGAN HIPERGLIKEMIA

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Abstrak

Hiperglikemia dan resistensi insulin adalah keadan yang sering dijumpai pada penderita kritis yang di rawat di ICU, walaupun tanpa disertai riwayat penyakit diabetes. Hiperglikemia harus segera dikendalikan oleh karena merupakan faktor resiko memperburuk luaran klinik akibat meningkatnya produksi *oxygen reactive species* (ROS). Tujuan penelitian ini adalah untuk mengetahui perbedaan terapi insulin intensif dengan terapi insulin konvensional terhadap peningkatan kadar *superoxside dismutase* (SOD) yang merupakan *surrogate marker* dari ROS, penurunan kadar TNF-α, IL-6, peningkatan kadar Albumin, dan kejadian SIRS.

Penelitian ini merupakan penelitian esperimental " *randomized pre and post test controle group design* " yang melibatkan 40 penderita dewasa yang dirawat di ICU RSUP. Sanglah Denpasar, dengan besar sampel dihitung dengan rumus Pocock. Kemudian dilakukan uji normalitas K-S, t test, t paired, dan Fisher's Exact test.

Dari penelitian ini didapatkan hasil yaitu: (1) Terdapat perbedaan bermakna terhadap peningkatan kadar rerata SOD pada kelompok terapi insulin intensif dan kelompok terapi insulin konvensional (370,70 vs 98,50 U/gHb; p=0.001); (2) Tidak terdapat perbedaan bermakna terhadap penurunan kadar rerata TNF-α pada kedua kelompok (2,98 vs 3,10 pg/ml; p=0.977); (3) Terdapat perbedaan yang bermakna terhadap penurunan kadar rerata IL-6 pg/dl (10,25 *vs* 2,02; p=0.023); (4) Terdapat perbedaan yang bermakna terhadap peningkatan kadar rerata albumin (0,62 *vs* 0,22); Terdapat perbedaan yang bermakna terhadap kejadian SIRS (10 % *vs* 40%, p=0.000)

Dari hasil penelitian ini dapat dibuat suatu kesimpulan yaitu pemberian terapi insulin intensif dengan menurunkan kadar gula darah pada level normoglikemia dapat meningkatkan kadar SOD, menurunkan sitokin inflamasi IL-6, dan memperbaiki luaran klinik oleh karena dapat meningkatkan kadar albumin dan menurunkan kejadian SIRS pada penderita kritis di ICU.

Kata kunci: Hiperglikemia, Terapi insulin intensif, Terapi insulin konvensional, SOD, Penderita kritis di ICU, Sitokin proinflamasi, Sindroma respons inflamasi sistemik, Albumin.

Latar Belakang Masalah

Penderita kritis/*critically ill patients* yang dirawat di instalasi rawat intensif (ICU) cenderung mengalami hiperglikemia, yang disebut *stress diabetes* atau *newly diabetes*. Hal ini disebabkan oleh karena pelepasan hormon anti regulasi seperti efinefrin, nor-efinefrin, katekolamin, dan *glucagons*. Hiperglikemia dapat meningkatkan ROS melalui proses enzimatik yaitu reaksi oksidasi dan fosforilasi (*ox-phos*) serta reaksi ADPH – *Oxidase*. Di samping dapat melalui proses non-enzimatik membentuk *gluco oxidant* dan *glycation.* SOD merupakan enzim yang berperan sebagai antioksidan bila terjadi produksi ion superoksida di mitokondria. Telah lama diketahui bahwa ada hubungan yang erat antara hiperglikemia dan gangguan fungsi imun terutama infeksi. Kelainan primer hubungan ini adalah karena adanya disfungsi dari sel fagosit. ROS yang terjadi pada hiperglikemia akan mengaktivasi faktor transkripsi NF-□B yang memicu produksi sitokin infalmasi seperti TNF-α dan IL-1. Sitokin inflamasi tersebut mempunyai efek otokrin dan parakrin dapat memicu produksi sitokin lainnya seperti IL-6, sehingga terjadi kaskade inflamasi secara sistemik. Inflamasi yang terjadi mengakibatkan penurunan produksi albumin di hati.

Insulin merupakan obat anti diabetes yang dianggap paling rasional saat ini, oleh karena mempunyai efek anabolik, namun ditengarai masih sering menimbulkan komplikasi serius seperti hipoglikemia. Di samping hal tersebut diatas, masih terjadi perebatan mengenai kadar gula darah yang harus dicapai dengan terapi insulin.

Metode Penelitian

Penelitian ini merupakan penelitian eksperimental dengan rancangan *" pre and post test control groupdesign"* pada kelompok terapi insulin intensif dan terapi nsulin konvensional.

Hasil dan Pembahasan

Kadar *Superoxide Dismutase* (SOD) pada Kelompok Terapi Insulin Intensif dan Kelompok Terapi Insulin Konvensional

Dari hasil penelitian ini, didapatkan kadar SOD rerata sebelum terapi insulin intensif adalah 1084,90 ± 193,43 U/gHb, dan sebelum terapi insulin konvensional adalah 1049,40 ± 166,58. Setelah perlakuan pada hari ke tujuh, kadar SOD terapi insulin intensif adalah 1455,60 ± 180,25 U/gHb, dan setelah terapi insulin konvensional adalah 1147,90 ± 165,42 U/gHb. Pada analisis uji *paired samples test*, terdapat peningkatan signifikan terhadap rerata SOD sebelum dan sesudah pemberian terapi insulin pada kedua kelompok (p=0,001). Hasil analisis uji t terhadap kadar SOD setelah diberikan terapi insulin intensif dan terapi insulin konvensional terdapat perbedaan bermakna dengan nilai p=0,001. Sedangkan, peningkatan nilai rerata SOD (Δ SOD) pada kelompok terapi insulin intensif adalah 370,70 ± 163,35 U/gHb, dan kelompok terapi insulin konvensional adalah 98,50 ± 96,14 U/gHb. Dari hasil analisis uji t, diperoleh perbedaan bermakna

terhadap peningkatan kadar Δ SOD kelompok terapi insulin intensif dengan kelompok terapi insulin konvensional (370,70 *vs* 98,50, p=0.001).

Dari hasil penelitian ini dapat disimpulkan bahwa, pada hiperglikemia terjadi produksi ion superoksida (ROS) yang berlebihan, sehingga akan memerlukan SOD yang banyak pula untuk meredam efek negatif dari stress oksidatif tersebut, dengan akibat kadar SOD menurun oleh karena konsumsinya meningkat. Setelah hiperglikemia ditanggulangi dengan insulin, maka produksi ROS akan berkurang sehingga kadar SOD kembali meningkat ke arah normal.

Kadar TNF-α pada Kelompok Terapi Insulin Intensif dan Kelompok Terapi Insulin Konvensional

Hasil pada penelitian ini didapatkan kadar TNF-α pada kelompok terapi insulin intensif sebelum diberikan perlakuan (*pre-test*) adalah 10,26 ± 7,22 pg/ml, sedangkan kadar TNF-α pada kelompok terapi insulin konvensional sebelum perlakuan (*pre-test*) adalah 8,15 ± 6,29 pg/ml. Hasil pemeriksaan yang didapatkan setelah perlakuan pada hari ke tujuh, didapatkan kadar TNF-α pada kelompok terapi insulin intensif adalah 7,28 ± 2,77 pg/ml, sedangkan pada kelompok terapi insulin konvensional adalah 8,78 ± 4,48 pg/ml. Setelah dilakukan analisis *paired samples test*, tidak didapatkan perbedaan penurunan yang bermakna baik pada kelompok terapi insulin intensif (p=0.078), maupun kelompok terapi insulin konvensional (p=0.713). Analisis selanjutnya, dilakukan uji t terhadap kadar TNF-α *post test* pada kedua kelompok. Hasil analisis tersebut, tidak terdapat perbedaan bermakna terhadap penurunan kadar TNF-α pada kedua kelompok (p=0.211). Sedangkan analisis uji t yang dilakukan terhadap nilai rerata (Δ TNF-α) pada kedua kelompok, juga tidak terdapat perbedaan bermakna pada kedua kelompok (2,98 *vs* 0.63, p=0.977).

Hal ini dapat disebabkan oleh karena sulitnya menentukan waktu yang tepat untuk mendeteksi keberadaan TNF-α secara pasti, tidak stabilnya TNF-α dalam darah simpan, dan beberapa faktor resiko eksogen seperti adanya sentral obesitas, konsumsi alkohol, dan faktor genetik tidak dikendalikan dengan baik. Selain itu produksi TNF-α dipengaruhi oleh banyak faktor, yaitu stresor dari penyakit yang mendasari hiperglikemia tersebut yang penanganannya belum mencapai hasil yang sempurna.

Kadar IL-6 pada Kelompok Terapi Insulin Intensif dan Kelompok Terapi Insulin Konvensional

Dari hasil pemeriksaan tersebut di atas didapatkan kadar IL-6 pada kelompok terapi insulin intensif sebelum perlakuan (*pre-test*) adalah 23,21 ± 9,63 pg/ml, sedangkan hasil kadar IL-6 pada kelompok terapi insulin konvensional *pre-test* adalah 20,35 ± 10,17 pg/ml. Hasil analisis uji normalitas Kolmogorov-Smirnov *test*, data kedua kelompok berdistribusi normal, dan dari hasi uji t, tidak didapatkan perbedaan bermakna pada kedua kelompok (p=0.366). Hasil pemeriksaan setelah perlakuan pada hari ke tujuh, didapatkan kadar IL-6 *post test* pada kelompok terapi insulin intensif adalah 12,96 ± 7,81 pg/ml, sedangkan pada kelompok terapi insulin konvensional *post test* adalah 18,32 ± 7,11 pg/ml. Dari data tersebut diatas didapatkan penurunan kadar IL-6 baik pada kelompok terapi

insulin intensif, maupun pada kelompok terapi insulin konvensional. Setelah dilakukan analisis uji *paired samples test*, didapatkan penurunan kadar IL-6 yang signifikan pada kelompok terapi insulin intensif (p=0.001), sedangkan hasil pada kelompok terapi insulin konvensional tidak didapatkan penurunan yang bermakna (p=0.411). Kemudian dilakukan analisis uji t terhadap kadar IL-6 setelah perlakuan pada kedua kelompok. Dari analisis tersebut didapatkan perbedaan yang bermakna antara terapi insulin intensif apabila dibandingkan dengan terapi insulin konvensional (p=0,001). Sedangkan analisis uji " t " terhadap penurunan nilai rerata kadar IL-6 (Δ IL-6) pada kedua kelompok, didapatkan perbedaan yang bermakna (10,25 *vs* 2,02; p= 0.023).

Perbedaan yang terjadi pada penelitian diatas, dapat disebabkan oleh karena pada kelompok terapi insulin konvensional gula darah dipertahankan masih dalam keadaan hiperglikemia (180 – 200 mg/dl), sedangkan gula darah pada kelompok terapi insulin intensif dipertahankan pada batas normal (80 – 110 mg/dl), sehingga produksi stress oksidatif masih lebih tinggi pada kelompok terapi insulin konvensional jika dibandingkan kelompok terapi insulin intensif. Sebagai akibat dari proses tersebutdi atas, produksi mediator inflamasi yang lebih tinggi pada terapi insulin konvensional.

Kadar Albumin pada Kelompok Terapi Intensif dan Kelompok Terapi Insulin Konvensional

Hasil pemeriksaan kadar albumin serum pada kelompok terapi insulin intensif sebelum perlakuan (*pre-test*) adalah 2,75 ± 0,58 mg/dl, sedangkan pada kelompok terapi insulin konvensional adalah 2,83 ± 0,43 mg/dl. Setelah diberikan perlakuan dengan terapi insulin, maka hasil pemeriksaan pada hari ke tujuh didapatkan hasil kadar albumin *post-test* pada kelompok terapi insulin intensif adalah 3,38 ± 0,40 mg/dl, sedangkan kadar albumin pada kelompok terapi insulin konvensional *post-test* adalah 3,06 ± 0,32 mg/dl. Pada analisis *paired samples test*, terdapat peningkatan yang bermakna baik pada kelompok terapi insulin intensif (p=0,001), maupun pada kelompok terapi insulin konvensional (p=0,001). Analisis uji t terhadap kadar albumin setelah (*post test*) diberikan terapi insulin pada kedua kelompok, terdapat perbedaan yang bermakna (p=0,009). Sedangkan analisis uji t terhadap peningkatan nilai rerata albumin (Δ albumin) pada kedua kelompok didapatkan perbedaan yang bermakna antara kelompok terapi insulin intensif bila dibandingkan dengan kelompok terapi insulin konvensional (0,62 *vs* 0,22; p=0.001).

Perbedaan tersebut diatas disebabkan oleh karena, hiperglikemia dapat menyebabkan meningkatnya permeabilitas pembuluh darah sehingga terjadi pergeseran albumin ke interstisiil dan terjadinya mikroalbuminuria. Selain itu hiperglikemia akan meningkatkan produksi stress oksidatif yang dapat menurunkan produksi albumin di hati.

Kejadian SIRS pada Kelompok Terapi Insulin Intensif dan Kelompok Terapi Insulin Konvensional

Dari data penelitian tersebut didapatkan kejadian SIRS pada kelompok terapi insulin intensif adalah 2 orang (10 %), sedangkan pada kelompok terapi insulin

konvensional adalah 9 orang (45 %). Setelah dilakukan analisis dengan *Fisher's Exact Test*, terdapat perbedaan yang signifikan terhadap penurunan terjadinya SIRS pada kelompok terapi insulin intensif apabila dibandingkan dengan terapi insulin konvensional (p=0,001). Selain itu, dilakukan analisis terhadap estimasi resiko terjadinya SIRS pada kelompok terapi insulin intensif dan kelompok terapi insulin konvensional. Hasil dari analisis tersebut didapatkan Rasio Odds pada terjadinya SIRS pada kedua kelompok adalah 0,136, dengan Interval Kepercayaan 0,025 – 0,748. Sedangkan Resiko Relatif terjadinya SIRS pada kedua kelompok adalah 0,222 dengan Interval Kepercayaan 0,055 – 0,902.

Hal tersebut di atas dapat disebabkan oleh karena pada kelompok terapi insulin konvensional, gula darah dipertahankan masih pada level hiperglikemia. Keadaan tersebut akan meningkatan produksi senyawa oksigen reaktif sebagai stress oksidatif. Stres oksidatif tersebut akan mengaktivsi NF-□B sehingga memicu produksi sitokin proinflamasi seperti TNF-α, IL-1, dan IL-6. Selain itu pada hiperglikemia dapat menyebabkan menurunnya fungsi fagositik dari sel fagosit.

Temuan Baru

Temuan baru yang dapat dikemukakan pada penelitian ini adalah sebagai berikut.

1. Memperkuat validitas data bahwa terapi insulin intensif pada penderita hiperglikemia dapat meregulasi gula darah secara cepat dengan target normoglikemia, sehingga dapat meningkatkan produksi antioksidan, menurunkan produksi IL-6, meningkatkan kadar albumin, serta dapat menurunkan kejadian SIRS
2. Enzim SOD sebagai anti oksidan meningkat lebih tinggi setelah pemberian terapi insulin intensif daripada terapi insulin konvensional.

Kesimpulan

Terapi insulin intensif pada penderita hiperglikemia lebih baik daripada terapi insulin konvensional, oleh karena dapat menurunkan produksi ROS lebih rendah, sehingga terjadi peningkatan kadar SOD lebih tinggi. Penurunan produksi ROS tersebut juga dapat menurunkan produksi sitokin inflamasi seperti IL-6, sehingga dapat menurunkan kejadian SIRS, memperbaiki permeabilitas pembuluh darah, sehingga dapat mengurangi kebocoran terhadap albumin, sehingga dapat memperbaiki luaran klinik penderita. Di samping itu tidak terdapat perbedaan bermakna terhadap terjadinya komplikasi hipoglikemia pada pemberian terapi insulin intensif.

Saran

1. Diperlukan penelitian lanjutan dengan metode yang sama untuk mengetahui peranan ROS terhadap produksi mediator lainnya seperti NO, ICAM, VICAM, dan VEGF yang diduga berdampak negative terhadap endotil.
2. Sebaiknya variabel yang diteliti diperiksa secara serial sesuai dengan adanya perbaikan ataupun perburukan penyakit yang mendasarinya,

sehingga di dapat data luaran klinik yang akurat terhadap hubungan sebab akibat dari variabel variabel tersebut.

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