# 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, cate cholamine, 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 compli cations 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-$\alpha$, the instability of TNF-$\alpha$ in blood, and such other risky factors as central obesity, alcohol consumption, and other uncontrollable genetic factors. Besides, TNF-$\alpha$ 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 ($\Delta$ 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 $2.75 \pm 0.58$ mg/dl, while it was $2.83 \pm 0.43$ on conventional insulin therapy group. The post-test result of albumin level on intensive insulin therapy group was $3.38 \pm 0.40$ mg/dl, while it was $3.06 \pm 0.32$ 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 ($\Delta$ 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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