Expressing Macrophage and Systemic Inflammatory Response In Early and Delayed Internal Fixation On Closed Femur Fracture

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ABSTRACT

Internal fixation is one of treatment modalities in fracture management. Recently, the early and delayed internal fixations still become debatable topics. The debate is resulted from the advance of surgery technique, anesthetic, and complication distinction.

Internal fixation will trigger macrophage to express inflammatory mediator from activated macrophage. The research aims are: (1) to know IL-1â and IL-10 -expressing macrophage before internal fixation procedure, and (2) to know the difference between the systemic inflammatory response after early internal fixation and delayed one.

The design of the study is *"post test only control group design".* All study activities were carried out at Central Hospital Denpasar and at BPPV Pegok Denpasar. Samples of this study were closed femoral fractures with internal fixation treatment. Materials that are examined includes (1) patient serum that was taken before and after internal fixation for examining IL-6 using ELISA method; (2) soft tissue biopsy that was taken during internal fixation for immunohistochemistry staining using IL-1â and IL-10 monoclonal antibody to see macrophage activity in expressing of IL-1â and IL-10.

Sample size was estimated by Pocock formula. Forty decided samples were divided into two groups, 20 person of treatment group (early internal fixation) and other 20 persons of control group (delayed internal fixation). Then, K-S normality test, t-test group, t-paired test, and correlation test were conducted. The result of the analysis was presented in table and narration.

The result shows that there is a significant lower of IL-1â -expressing macrophage at first day (day I) than at third –fifth day (day III-V) (2.37±2.98 %, vs 4.99±4.89 %, p<0.05). Another result shows that serum IL-6 after internal fixation at first day (early) significantly lower than that third-fifth day (delayed) (51,17± 23,19 pg/ml vs 95,39± 80 pg/ml, p<0.05).

From this study, can be concluded that: (1) there is lower local inflammatory reaction at early internal fixation than delayed one and (2) the increase of serum IL-6 before and after internal fixation at first day (early) significantly lower than that third-fifth day (delayed), and serum IL-6 before internal fixation can be used as a predictor of serum IL-6 after internal fixation.

***Key words**: Early internal fixation, delayed internal fixation, IL-1â –expressing macrophage, systemic inflammatory response.*

1. INTRODUCTION

Internal fixation is one of modalities in fracture treatment. According to STEER (Succint and Timely Evaluated Evidence Review) analysis, early internal fixation is clinically more beneficial than the delayed one [1'2]. Recently, that procedure is still under debate especially concerning early total care, damage control and delayed total care.

Johnson (1985) reported that an internal fixation on a major fracture with a delay more than 24 hours would cause a five times increase in occurrence of ARDS (Adult Respiratory Response Syndrome) as a complication [3]. On an isolated femoral fracture, a 10% incidence of fat embolism syndrome will occur if the fixation is delayed after 10 hours and 0% if it is done before that [4]. Other researcher reported that pneumonia incidence in early internal fixation on femur fracture was 10%, however in delayed one was 38 %. This rate increased if associated with chest trauma unto 14% in early internal fixation and 48% in delayed one [5].

These facts are due to innate immunity activation which is in synergy with the lost of tissue barrier function [6]. The innate immunity in the form of systemic inflammatory response if it occurs prolongs and

excessively will cause a Systemic Inflammatory Response Syndrome (SIRS). However, up till now the difference local inflammation and systemic inflammatory response between during early internal fixation and the delayed one is not adequately understood.

Death rate due to MOD/MOF is still high, therefore prevention is an important measure in dealing with SIRS/MOD. Preventive measure by administrating drugs such as corticosteroids, monoclonal antibodies (anti-endotoxin antibodies, TNF antagonis, IL-1 ra), etc has been tried but did not bring unsatisfactory results [7].

Natural history of trauma (in this case, a fracture) depends on the degree of first damage (first hit), body biological response (influenced by genetic constitution, age, sex, underlying illness) and modality of treatments (second hit). From these 3 factors, only the modality of treatment (fracture fixation) can be modified and used as preventive measure, such as damage control orthopaedic, with early total care or delayed total care, thus reduce biological burden is due to trauma [8].

To reduce post-internal fixation's complications, types of procedure (fixation methods) and timing of procedure can be considered as preventive measures. In early internal fixation, the body is expected able to cope by giving adequate response, either locally or systemically.

Macrophage is a primary immune cell which produces local cytokine in tissue and in severe trauma macrophage often suffers alteration in cellular immune response [9]. With the difference in timing for internal fixation, the early or the delayed one, physiologically there are changes in macrophage's micro environment which cause alteration on macrophage's activation. Macrophage's activation needs contact between ligand and receptor [10]. Surgeon, while doing internal fixation will manipulate tissue, therefore creating more tissue damage. This condition will induce the pre-activated macrophage to express inflammatory mediators which give influence on either local inflammatory response or systemic.

This research has purposes to understand the difference between local tissue inflammatory response on fracture (macrophage which expresses IL-1 â and IL-10) in early internal fixation and delayed one, also to understand the difference between the increase of systemic inflammatory response (IL-6 as the marker) due to early internal fixation and delayed one on closed femur fracture.

2. METHOD

This is a quasi experimental study with *"post-test only control group design"* [11]. All procedures were approved by committee on ethical clearance of School of Medicine Udayana University

Sample: patients with closed simple femur fracture which fulfilled inclusion criteria.

Eligible samples: sample obtained after eliminated cases with exclusion criteria.

Inclusion criteria:

1. Patients with closed simple femur fracture without trauma/fracture at other body site.
2. Age 14-60 years old.
3. In healthy condition before accident happened.

Exclusion criteria:

1. Hgb < 10 gr%
2. Has ever been shocked and recognized in hospital evaluation.
3. Patients with closed simple femur fracture whom will be treated conservatively
4. Unwilling to become member of study's subject.

There were 20 cases was done early and 20 case was done delayed internal fixation. To avoid biases, the researcher will gather the sample using *permuted block random sampling* and the sample will be divided into early internal fixation group and delayed one.

OPERATIONAL DEFINITIONS FOR VARIABLES

1.IL-1â - expressing macrophage is the percentage of IL-1â - expressing macrophage (number of IL-1â - expressing macrophage in 100 macrophage cells) which is counted from soft tissue biopsy surround fracture site which is taken during surgery and stained with immunohistochemistry staining using monoclonal antibody against IL-1â.

2.IL-10 - expressing macrophage is the percentage of IL-10 - expressing macrophage (number of IL-10 - expressing macrophage in 100 macrophage cells) which is counted from soft tissue biopsy surround fracture site which is taken during surgery and stained with

immunohistochemistry staining using monoclonal antibody against IL-10.

3.Timing for internal fixation: Timing for internal fixation consists of 2 unseparated components as follows: time component, it is the time from fracture-causing injury unto the time on doing internal fixation procedure, and internal fixation procedure component itself. Internal fixation procedure will be done by using standard protocol that is lateral incisión and application of plate and screw. As independent variable the timing for internal fixation is divided unto timing for internal fixation in intervention and controls one. So timing for internal fixation is defined as follows:

i. Timing for internal fixation as intervention is an internal fixation which is done within 24 hours after fracture-causing injury (day I). This intervention is defined as early internal fixation.

ii. Timing for internal fixation as control is an internal fixation which is done at day III-V of fracture-causing injury. This control is defined as delayed internal fixation.

4. Systemic inflammatory response is an increase on systemic inflammatory response by measuring IL-6 serum concentration from venous blood pre- and post-internal fixation, IL-6 concentration is measured using sandwich ELISA method (pg/ml).

5.Closed simple femur fracture is a discontinuity of femur without any laceration on skin surrounds broken bone with simple transversal fracture's line which can be evaluated by using plain radiograph.

3. RESULTS

3.1 Subject Chaacteristic

Table 3.1: *Subject Characteristic*

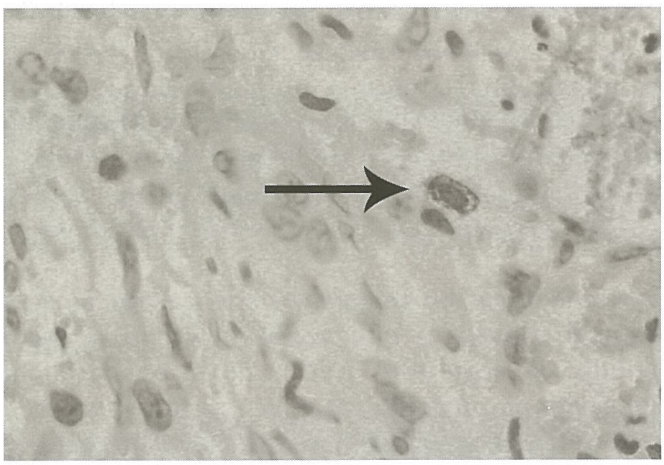
Characteristic		Intervention group (early)(n=20)(Mean±SD)	Control group (delayed)(n=20)(Mean±SD)	p
Sex:	M	14	14	0,634
	F	6	6	
Age (year)		27,8±11,47	25,2±10,59	0,461
Causes	1. Traffic accident	20	18	0,349
	2. Fall from tree		1	
	3. Household accident			
	4. etc		1	
Diagnosis of femur fracture: Fracture's line				
	1. Simple tranverse/oblique	12	17	0,078
	2. Butterfly	8	3	
Hgb. Pre-internal fixation (g%)		12,91±1,92	11,8±1,28	0,038
Amount of bleeding (ml)		360,5±219,676	352,5±202,27	0,905
Duration of procedure (hour) :		1,15±0,488	1,26±0,487	0,474
IL-1â serum concentration pre-internal fixation (pg/ml)		0,917±0,757	0,892±1,343	0,123
IL-1ra serum concentration pre-internal fixation (pg/ml)		639,94±503,47	911,22±768,71	0,195
IL-6 serum concentration pre-internal fixation (pg/ml)		25,85±13,68	29,16±32,00	0,674

3.2 Macrophage analysis in Early Internal Fixation (Intervention group) and Delayed One (Control group)

Table 3.2 IL-1â – expressing macrophage dan IL-10

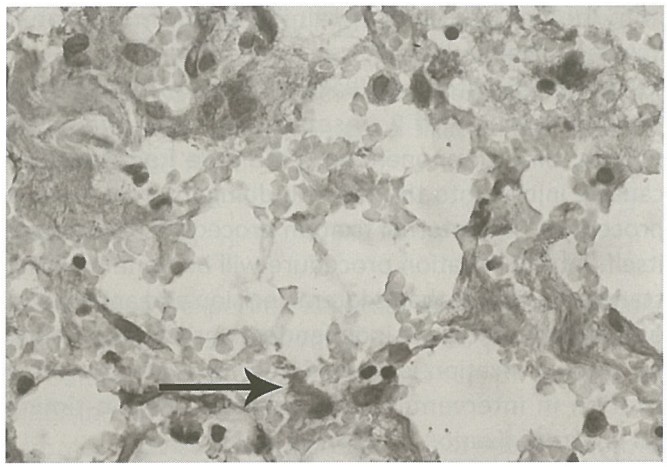
Characteristic	Intervention group (early) (n=20) (Mean±SD)	Control group (delayed) (n=20) (Mean±SD)	p
IL-1â – expressing macrophage (%)	2,37±2,98	4,99±4,89	0,047
IL-10 – expressing macrophage (%)	3,04±3,35	5,41±6,07	0,135

There is a significant difference between IL-1â – expressing macrophage in early internal fixation group and delayed one (mean 2,37% *vs* 4,99 %, p=0,047). However there was no significant difference seen between IL-10 – expressing macrophage in early internal fixation group and delayed one (mean 3,04±3,35 *vs* 5,41±6,07 %,p=0,135) (Table 5.2).



Picture: 3.1 *Soft tissue biopsy around fracture site with imunochemestry stained with IL-1 â Monoclonal Antibody. X 400 (positive reaction with brown cytoplasm)*

From bivariate correlation analysis we found that macrophage which expresses IL-1 â did not associate with IL-1 â serum, IL-1ra serum and IL-6 serum (p>0,05). The same thing also occurred with IL-10 – expressing macrophage (p>0,05). At tissue level IL-1â – expressing macrophage had significant association with IL-10 – expressing macrophage (r=0,582, p=0,000).



Picture : 3.2 *Soft tissue biopsy around fracture site with imunochemestry stained with IL-10 Monoclonal Antibody. X 400 (positive reaction with brown cytoplasm)*

Table 3.3 *Pearson's Bivariate Correlation between Macrophage (which expresses IL-1â and IL-10) and IL-1â serum, IL-1ra serum, IL-6 serum*

Variable		IL-1â – expressing macrophage	IL-10 – expressing macrophage
IL-10 – expressing macrophage	r	0,582	
	p	0,000	
IL-1â serum concentration	r	0,278	0,112
	p	0,083	0,492
concentration	p	0,722	0,681
concentration	p	0,432	0,363

3.3 IL-6 serum concentration analysis, pre- and post-internal fixation in intervention and control groups.

There was a significant difference in IL-6 concentration between early internal fixation group and delayed one (51,17 *vs* 95,39; p=0,027) (Table 3.4).

Corrected model p<0,05

This model was adequate in predicting IL-6 serum post-internal fixation because the significance of corrected model was far below 0,05. Table 3.6 shown that IL-6 serum concentration pre-internal fixation was different significantly from IL-6 serum concentration post-internal fixation (p<0,05) and it can be said that IL-6 serum concentration pre-internal fixation is able

Table 3.4
Increase of IL-6 serum concentration pre- and post- internal fixation in early internal fixation and delayed one

IL-6 serum concentration	Early I.F. (Intervention group) (n=20) (Mean±SD)	Delayed I.F. (Control group) (n=20) (Mean±SD)	P
Pre-internal fixation	25,85±13,68	29,16±32,00	0,672
Six hours post-internal fixation	51,17±23,19	95,39±80,29	0,027
The increase between pre- and post- internal fixation	25,32±22,30	66,22±65,42	0,014

Table 3.5
IL-6 serum concentration pre- and post- internal fixation in early internal fixation and delayed one

Groups	Pre-	Post-	P
Intervention group (early)	25,85±13,68	51,17±23,19	<0,01
Control group (delayed)	29,16±32,00	95,39±80,29	<0,01

There were significant difference in IL-6 serum concentration pre- and post- internal fixation from each group (p<0,01).

Table 3.6
Univariate General Linear Model Analysis on Hgb., IL-1â , IL-1ra, and IL-6 pre-internal fixation toward IL-6 post-internal fixation

Independent variables of IL-6 post-internal fixation	
Independent variables	P
Haemoglobin	0,984
IL-1Ra serum concentration pre-internal fixation	0,584
IL-1â serum concentration pre-internal fixation	0,855
IL-6 serum concentration pre-internal fixation	0,000
Groups (early internal fixation or delayed one)	0,049

to predict IL-6 serum concentration post-internal fixation. Table 3.6 also shown the significant difference between groups (intervention and control) with p <0,05 which means that the difference between group is able to differentiate IL-6 serum concentration post-internal fixation.

DISCUSSION

TISSUE MACROPHAGE SURROUNDING FRACTURE

IL-1â - expressing macrophage between intervention (early internal fixation) and control (delayed internal fixation)

From this study we found that the percentage of IL-1â - expressing macrophage in early internal fixation is significantly different from the delayed one (p<0,05) (Table 3.2).

The similar result was also shown by Einhorn (1995) who used Sprague-Dawley mouse whose legs were made broken [14]. Then the tissue surround fracture site was cultured at day III and then stimulated with M-CSH. Macrophage shown a high level of activity. So, tissue macrophage at fracture site shows high activity level at day III. Ogura (1999) reported that the peak for priming index occured at day II-V [15].

Macrophage activation depends on tissue micro environemnt. If there is trauma or fracture, the body will respond through homeostasis proses as physiological process through neurologic, immunologic and metabolic responses [16]. Fracture acts as inflammatory focus are due to necrotic tissue, ischemic tissue surrounded by hypoxic tissue [17]. This tissue damage is a danger signal so inflammatory process may occur. In the cellular immune response, macrophage is a very important cell and it will be activated by that danger signal. Macrophage activation classically need signal as INF-ã through INF-ã-R to express pro-inflammatory mediators [18]. In cardiac surgery IFN-ã decreases on the first few days so there is not much macrophage activation through classic pathway and backs to normal again at day III-V [9]. Therefore active macrophage classically higher at day III-V. On trauma TLR-2 and TLR-4 will act to increase inflammatory response [19].

At inflammatory process, if the homeostasis is achieved, the PMN will go through apoptosis process and its number will decrease on day III-V and its

function is replaced by macrophage [20]. In his study, Daley (2005) who used neutropenic mouse and made incision on it, found that PMN in the wound was 100 times lower than control, afterward he analyzed the supernatant from wound oozing fluid and found that the pro-inflammatory cytokine was higher than the control (TNF 68%, IL-6 168%, TGF 61%), but no IL-10 [21]. From those studies we conclude that the inhibition of pro-inflammatory cytokine production by PMN's products will cause inhibition on macrophage activation which might be due to PGE2. Since the PMN at fracture site on day I is more than day III-V, thus the macrophage activation on day III-V is higher than day I which is shown by the higher percentage of macrophage which expresses cytokine.

In his study, Browder (1990) administered glucane (a macrophage stimulator) on severe trauma case which would undergo surgery and he found a significant increase of IL-1â serum concentration on day III compared to control (143±19,3 pg/ml compared with 78,6±11,7 pg/ml, $p < 0,05$) and this difference seem to be related to macrophage activation [22]. Browder's study supports our result which as shown by a significant difference ($p<0,05$) between the percentage of IL-1â - expressing macrophage in early internal fixation (day I or intervention group) and delayed one (day III-V or control group).

From the result of this study and statistical analysis, it is proven that IL-1â - expressing macrophage on intervention group is lower than control group.

IL-10 - expressing macrophage between intervention (early internal fixation) and control (delayed internal fixation)

IL-10 - expressing macrophage in intervention group was found with mean= 3,04±3,35 % and in control group with mean= 5,41± 6,07%. Analyzed with t-test we found no significant difference between early internal fixation group and the delayed ($p>0,05$) (Table 3.2).

Data above actually shows the difference in IL-10 - expressing macrophage between early internal fixation and the delayed one by 1 against 2, however statistically that difference is not significant ($p>0,05$). This may be due to small sample size or due to macrophage activation which depend on micro environment of injured tissue. In the beginning of trauma, PMN is much found in surround injured tissue and well known that the product of PMN such as PGE2 will suppress the production of pro-inflammatory mediators, but it does not suppress IL-10 since PGE2 will increase IL-10 and suppress IL-12 so indirectly will reduce pro-inflammatory cytokine [23'21]. In cardiac surgery it can be observed also a decrease in IFN-ã on the first few days because of the decreased in IL-12 so there is not much macrophage activation through classical pathway and will be back to normal again on day III-V [9]. Above condition seems to give more influence to pro-inflammatory cytokine production.

The mean of IL-10 – expressing macrophage is higher on day III-V than day I. This condition is in one accord with IL-1â – expressing macrophage. In homeostasis state, IL-10 – expressing macrophage will show a significant difference in both groups a long with IL-1â – expressing macrophage because IL-10 is a cytokine regulator and also a compensation cytokine. This can be seen clearly from the correlation between IL-10 – expressing macrophage and IL-1â – expressing macrophage which is strong and significant ($p<0,05$) (Table 3.3) and it is presume that IL-10 inhibits IL-1â production from macrophage in otocrine or paracrine way and vice versa.

This study has proved that IL-1â – expressing macrophage is higher significantly on day III-V compares to day I, but this does not happen for IL-10 – expressing macrophage. This finding shows that the function of active macrophage alternative type as a regulator or compensated cytokine to reach homeostasis is inhibited [18]. This depends on micro environment which is more predominant in determining macrophage activity, therefore occasionally the balance between pro-inflammatory and anti-inflammatory is not reached, which local tissue is more pro-inflammatory so macrophage activation through classical pathway with pro-inflammatory cytokines is more dominant [24]. From this we can see that pro-inflammatory and anti-inflammatory cytokines do not always work in parallel but depend verily to the need, which is why in this study IL-10 – expressing macrophage does not show a significant difference between intervention group and control one.

From data and discussion, it can be seen that the study cannot prove if there is any significant difference between IL-10 – expressing macrophage in both intervention and control groups.

SYSTEMIC INFLAMMATORY RESPONSE POST-INTERNAL FIXATION.

Systemic Inflammatory Response (IL-6) post-Early Internal Fixation (intervention) and Delayed one (control)

From this study, IL-6 serum concentration at 6 hours post-internal fixation in intervention and control groups were 51,17± 23,19 pg/ml and 95,39± 80,29 pg/ml, respectively. And t-test showed a significant difference between groups (p<0,05).

The difference between early internal fixation (intervention) and delayed one (control)is only on timing to do internal fixation which is early internal fixation will be done on day I and the delayed one on day III-V. From previous discussion it has already been said that in early internal fixation, IL-â – expressing macrophage was lower than delayed one which is a sign for tissue inflammatory reaction. Eventhough the same procedure is applied to both groups but the systemic response was different between groups which is early internal fixation (intervention) group caused lower increase to IL-6 compared to delayed one (p<0,05).

Using univariate of variance analysis (Univariate General Linear Model) (Table 3.6), in this study we found that the difference between groups (the difference in internal fixation timing) will cause a significant difference (p<0,05) in IL-6 serum concentration post-internal fixation. Means that IL-6 serum concentration post-internal fixation in intervention group is different from the control group. This finding can be explained as follows. Higher macrophage activity on day III of fracture has been studied by Einhorn [14] . Ogura in 1999 reported that the peak of priming index occured at day II-V [15]. Daley (2005) in his experiment using neutropenic mice found that PMN product inhibited the production of pro-inflammatory cytokine [21]. Those 3 findings along with maximum tissue swelling at day III-V cause a relative ischemia on surround healthy tissue and internal fixation procedure will cause more hypoxic and acidotic condition which induce more inflammatory mediators [25].

Instead of that, when the tissue swelling badly, technically the surgery will be difficult, will be difficult to retract tissue, difficulty in hemostasis and the swelling tissue will press the surrounding healthy tissue and causing more ischemia at wound closure. So the tissue macrophage due to tissue ischemia will induce pro-inflammatory mediators production (i.e., IL-6) and then these mediators will enetr into circulation [25]. This condition can be observed in this study, the rise of IL-6 serum concentration in control group is higher than intervention one.

By this finding it can be proved that delayed internal fixation on day III-V (control group) will give more inflammatory response (in this case by measuring IL-6 serum concentration) compared to early one (intervention group). In other way early internal fixation (intervention group) will give less increase on inflammatory response (in this case by measuring IL-6 serum concentration) compared to the delayed one.

Association between Hgb., IL-1â Serum, IL-1Ra Serum dan IL-6 Serum pre-Internal Fixation with Increase on Systemic Inflammatory Respons

The success of surgical procedure generally depends on many factors, especially peri-operative factors such as pre-operative state, during operation and post-operative factors. Instead of surgical procedure itself (secondary insult), the magnitude of inflammatory response assumed depends on complex interaction between pro-inflammatory and anti-inflammatory mediators [26].

At fracture, bone and soft tissue are damaged and will cause local inflammatory response which the extent depends on the magnitude of tissue damage [27]. This local tissue damage will induce macrophage and its inflammatory response will induce systemic response which is in the beginning it is used for body's protection so the damage is localized [28]. However whenever the systemic response goes too far and becomes excessive, it will create systemic inflamation response syndrome [29].

IL-1â - expressing macrophage before internal fixation has a significant difference between those intervention and control groups (Table 3.2). It is well known that IL-1â – expressing macrophage has tendency to correlate with IL-1â serum concentration (p=0,083) (Table 3.2). It means that actually IL-1â also differs significantly from the groups yet with p <0,10.

From Univariate General Linear Model analysis (Table 3.6) we can see that Hgb did not influence IL-6 serum concentration post-internal fixation (p>0,05). On the contrary IL-6 pre-internal fixation had positive correlation to IL-6 serum concentration post-internal fixation (p<0,05). This finding can be interpreted as the higher IL-6 serum concentration pre-internal fixation is, the higher also IL-6 serum concentration post-internal fixation. In other words, IL-6 serum concentration pre-internal fixation may predict IL-6 serum concentration post-internal fixation. It seems it is due to the nature of IL-6 as good inflammatory marker so at higher inflammatory state, IL-6 as systemic inflammatory response marker post-internal fixation is also higher. This can be seen clearly in control group where there is a different micro environment in pro-inflammatory tissue which is shown as higher IL-1â – expressing macrophage (p<0,05), and mean of IL-6 serum concentration pre-internal fixation in that group also higher, which is 29,16±32,00 pg/ml vs 25,85±13,68 pg/ml.

Once more from Univariate General Linear Model analysis (Table 3.6) we found that the difference in groups (intervention/early vs control/delayed) cause the difference in IL-6 serum concentration post-internal fixation (p<0,05). This difference is caused by the difference in priming and IL-1â – expressing macrophage from both groups. IL-1â – expressing macrophage is a sign for cellular immune response toward tissue damage which is more pro-inflammatory in nature. The increase in this variable shows the increase on inflammatory process which signs as vasodilatation, an increase of vascular permeability, chemotaxis, and the production of inflammatory mediators such as cytokine. Inflammation will cause tissue swelling which causing ischemia upon healthy tissue surround it[25]. Control group seems more pro-inflammatory in nature.

In control group when internal fixation was done, tissue swelling became maximal so tissue manipulation during surgery caused more tissue damage and induced more IL-6. This can be seen from the result which IL-6 serum concentration post-internal fixation in control group was higher than intervention one. Previous data showed that IL-6 serum concentration was related to the extent of tissue damage, including tissue damage due to surgical procedure [30].

From the discussion above we may assume that the difference between systemic inflammatory response (IL-6) post-internal fixation in intervention group and control one is due to the changes in micro environment and the difference in tissue damage due to fixation. The changes in micro environment consist of difference in local inflammatory response and difference in immuno-competent cell priming. Internal fixation procedure will worsened or create more damages and induce the inflammatory mediators. The extent of expression from those mediators depends on the extent of tissue damage, the condition of micro environment, priming and tissue swelling.

Therefore from the result of this study and supported by the discussion above we find that IL-1â - expressing macrophage is higher in control group which means the more active inflammatory process. That condition is accompanied by priming which is maximal on day III-V, and internal fixation is a surgical procedure which may worsened tissue damage and induce more IL-6 serum in control group.

CONCLUSION AND SUGGESTION

CONCLUSION

An experimental study of pre- and post- internal fixation on closed femur fracture gave results as following:

1.IL-1â- expressing macrophage in early internal fixation is lower than dealyed one.

2.There is no difference between IL-10 - expressing macrophage in early internal fixation and delayed one.

3.Systemic inflammatory response (IL-6) post-internal fixation is lower in early internal fixation than delayed one

Therefore from the result of this study and supported by discussion, we conclude:

1.Inflammatory reactions surround fracture location is lower in early internal fixation compare to delayed one.

2. IL-6 serum concentration post-early internal fixation is lower than the delayed one and IL-6 serum concentration before internal fixation can be used as predictor for IL-6 serum concentration after internal fixation.

SUGGESTION

1.Based on the knowledge that the systemic inflammatory response (IL-6 serum concentrations) after early internal fixation of femur fracture are lower than the delayed ones thus in managing femur fracture, it is suggested that internal fixation procedure should be done on the first day or at least before day-3 after injury to reduce difficulty on doing procedure and complication.

2. May the biomolecular experts or chemist be able to find way to measure IL-6 serum concentration in quick way and cheap so IL-6 serum concentration can be used as systemic inflammatory response predictor for post-internal fixation routinely at trauma centre.

3. There is a need for studies on association between IL-6 serum concentration with severity of SIRS to determine how bad SIRS is and how the internal fixation can be done so that it can prevent the occurrence of MOD and MOF

4. Need the same study, yet with different Injury

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