

# The Role of Interleukin-6 (IL-6), Interleukin-10 (IL-10), Plasminogen Activator (PAA), and Plasminogen Activator Inhibitor (PAI) Towards the Occurrence of Peritoneal Adhesions in Post-Laparotomic Patients

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## ABSTRACT

**Background:** Peritoneal adhesion is still becoming one of the most common postoperative complications which increases the rate of morbidity and mortality. The process which leads to the formation of peritoneal adhesion is depending on the balance between the pro-inflammatory and anti-inflammatory processes, in which there are roles of Interleukin-6 (IL-6) and Interleukin-10 (IL-10) as well as the balance of fibrinolysis process played by Plasminogen Activator (PAA) and Plasminogen Activator Inhibitor (PAI).

**Objective:** This research is to study the relationship between the ratio of IL-6 to IL-10, as well as the ratio of PAI to PAA with the incidence of peritoneal adhesion after laparotomy procedure.

**Method:** The study was conducted using comparative experimental case study by treating two randomly selected groups using *randomised controlled trial* method. Group 1 was patients who underwent laparotomy procedure and were given *ketorolac tromethamine* which is analgesic that had anti-inflammatory effects, compared to group 2 which act as a control group and were given

*tramadol*, a pure analgesic drug. The subjects of this study were patients who undergoes stoma procedures (colostomy, ileostomy) due to colon perforation as a result of trauma or other diseases

**Results:** Correlation analysis that was conducted revealed significant interaction between IL-10 with PAA while there were no significant association recorded between IL-10 with IL-6 and PAI as well as IL-6 and PAA.

**Conclusions:** There is a significant interaction between the levels of IL-10 and PAA with the occurrence of peritoneal adhesion in post-laparotomy patients.

**Keywords:** IL-6; IL-10; PAI; PAA

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## BACKGROUND

With the development of knowledge on molecular biology, the mechanism of pathophysiology at bio-molecular level is also readily available. This involves the intrinsic signalling pathway system including the inflammatory system and the coagulation system which gives scientists a better understanding on cell responses towards injury.<sup>1,2</sup> Immediately after suffering an injury, the injured cells will produce cytokines, for example; Interleukin-1 (IL-1), Interleukin-2 (IL-2), TNF- $\alpha$ , interleukin-6 (IL-6), *Transforming Growth Factor-Beta* (TGF- $\beta$ ), all of which stimulate the healing process via the formation of early adhesion from fibrin deposits that had covered the injury spot.<sup>3,4,5</sup> After the subsiding of adhesion formation stimulus, anti-inflammatory cytokines such as; Interleukin-4 (IL-4) and Interleukin-10 (IL-10) will be produced by mesothelium cells to start fibrinolysis. These anti-inflammatory cytokines will stimulate the activity of *Plasminogen Activator Activity* (PAA) which will lyse fibrin and fibrin adhesion. The activity of *Plasminogen Activator Inhibitor* (PAT) on the other hand will be reduced due to the effect of anti-inflammatory cytokines and the reduce activity of pro-inflammatory cytokines.<sup>6</sup> Thus, when the incidence of peritoneal inflammation subsides, fibrinolysis will occur to reduce the formation of adhesions in the peritoneal cavity. Hence, the events of peritoneal healing is a dynamic process influenced by the concentration of cytokines inside the peritoneal cavity and the cytokine profiles indicate the actual process whether the adhesion formation is happening or not.<sup>5,7</sup> Peritoneal adhesion is still a problem in patients with postoperative laparotomy, where there is high rates

of morbidity and mortality reported annually.<sup>8</sup> Several studies prove the existence of extracellular signalling mediators, especially IL-6 which acts as an *adesiogenic*, while IL-10 acts as an *anti-adesiogenic*.<sup>9</sup> In the process of permanent peritoneal adhesion, the role of plasminogen activator (PAA) is known in the process of fibrinolysis whereas the adhesions effects can be adversely inhibited by plasminogen activator inhibitors (PAI). It is expected that this study will give an insight on the correlation ratio of perioperative IL-6 to IL-10 and PAI to PAA as well as its role in the occurrence of peritoneal adhesion.

## METHOD

This research is a correlation study with a *Randomized Control Trial* design, by treating two randomly chosen group using per mutable random method. All patients that underwent laparotomy procedures were divided into two groups. Patients in Group 1 were given *Ketorolac Tromethamine*, an analgesic that has anti-inflammatory effects, whereas Group 2 acted as a control group and was given *Tramadol*, a pure analgesic drug. In both treatments, several variables will be measured and act as an independent variable, namely the levels of Interleukin-6, Interleukin-10, Plasminogen Activator, and Plasminogen Activator Inhibitor. In the third month after surgery, the adhesion score will be measured which will be the responding variable.

## RESULTS

By using path correlation analysis, the results obtained in both groups are illustrated in the diagrams below

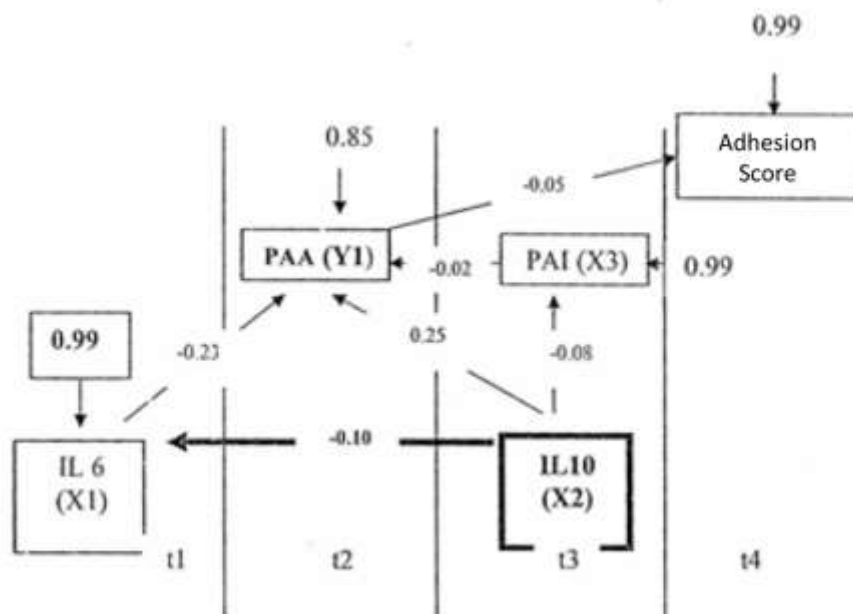


Figure 1. The results of correlation analysis of IL-6, IL-10, PAA and PAI towards the occurrence of adhesion in group treated with *ketorolac*

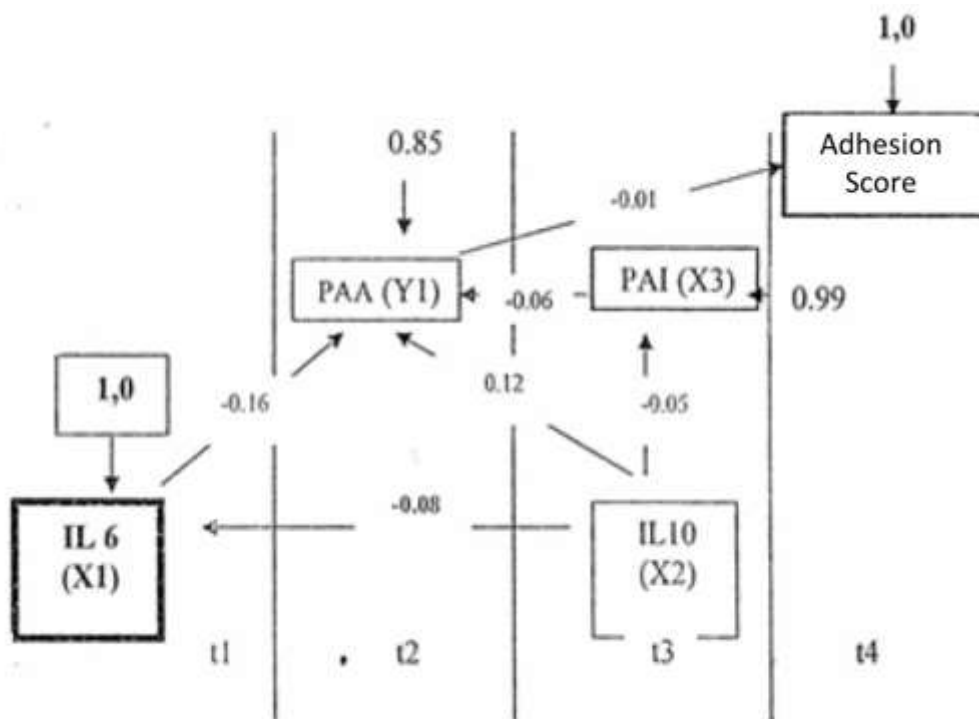


Figure 2. The Results of Correlation Analysis of IL-6, IL-10, PAA and PAI towards the Occurrence of Adhesion in Control Group

The path correlation analysis in Figure 1 and Figure 2 shows that there is a negative relationship between the IL-6 and PAA in both groups where the negative correlation is much stronger in *ketorolac*-treated group. IL-10 on the other hand is negatively correlated with both IL-6 and PAA. However, there is a positive correlation of IL-10 with PAA where the effect is smaller in control group as compared with the treatment group. The effect of PAI on PAA of patients with *ketorolac* treatment was weak negative, where the effect was only slightly stronger in the *ketorolac* group as compared to the control group.

### DISCUSSION

Figure 1 and Figure 2 show that there is a negative path correlation between IL-6 and PAA which means that a decrease in IL-6 levels will be accompanied by an increase in the PAA in patients who have been treated with *ketorolac*. The increment in PAA levels will then be followed by a decrease in the degree of adhesion in

patients who have been given *ketorolac* treatment. The results also show that IL-10 has a negative influence on both IL-6 and PAI which shows that IL-10 can suppress the production of IL-6 and PAI. IL-10 however has a positive effect on PAA that indicates an increase in IL-10 levels will tend to be followed by an increase in PAA levels in patients treated with *ketorolac*. The effect of PAI on PAA of patients with *ketorolac* treatment is weak negative where an increase in PAI levels will be followed by a slight decrease in the patient's PAA level. These results indicate that IL-10 can interact with IL-6 and PAI where an increase in IL-10 will be followed by a decrease in IL-6 and PAI, so there is a direct or indirect relationship to Plasminogen Activator Levels. The increase in IL-10 levels will lead to the increment in PAA level which plays a vital role in the process of fibrinolysis and will reduce adhesion. The administration of *ketorolac* reinforces the modulation of IL-10 and confirms all previous studies that peritoneal adhesion is highly dependent on the dynamic

balance between IL-6 and IL-10 which also affects the balance of the plasminogen activator with its inhibitors in the process of permanent peritoneal adhesion.<sup>3,4,5</sup>

## CONCLUSION

In the process of the occurrence of adhesion, cytokines IL-10, IL-6, and PAA and PAI have an interaction role where

IL-10 has a negative interaction with IL-6 and PAL but has a positive interaction with PAA. PAI on the other hand has a negative interaction against PAA which leads to the reduction of the occurrence of peritoneal adhesion.

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