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A prospective randomized pilot study of steroid modulation of cytokine (Interleukin 6) release in unilateral total knee replacement surgeries

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Abstract

Several studies evaluating the patients undergoing joint replacement have found elevation in the levels of cytokine interleukin-6(IL-6). High level of IL-6 after the major surgeries have been linked to postoperative fever, confusion, pain, acute respiratory distress syndrome, fat embolism syndrome. Pre and post-operative administration of low dose steroid (Inj. Hydrocortisone 100mg) in patients undergoing TKR has shown to reduce the interleukin-6 level and its complications.

The purpose of this study was to observe the effect of intravenous hydrocortisone on cytokine Interleukin-6 (IL-6) as primary outcome and also to observe presence of Fever, Blood sugar level (BSL), Pain score (using Visual analogue scale), Range of motion (ROM) and SpO₂ (Saturation of oxygen) as a secondary outcome in the patients undergoing unilateral total knee arthroplasty.

In our study 30 Patients were randomized into 2 groups. The study group received first dose of injection hydrocortisone 100mg I.V at the start of surgery followed by two more doses given eight hours apart while the control group received 100 ml of NS at similar intervals.

From this study, we conclude that a low dose of hydrocortisone given for a short period of over 24 hours perioperatively to the patients having unilateral total knee arthroplasty are associated with decreased level of inflammatory marker, the cytokine Interleukin-6 (IL-6). The benefits included decrease pain scores, better saturation of oxygen (SpO₂), lower prevalence of fever and better range of motion.

Keywords: Cytokine (Interleukin 6), Unilateral Total Knee Replacement

1. Introduction

The total knee arthroplasty (TKA) is a successful modality in treating severe osteoarthritis of knee joint and has improved the quality of life of patients with severe knee pain and difficulty in performing activities of daily living. Several studies evaluating the patients undergoing joint replacement have found elevation in the levels of cytokine interleukin-6(IL-6) [1, 2]. High level of IL-6 after the major surgeries have been linked to postoperative fever, confusion, pain, acute respiratory distress syndrome, fat embolism syndrome [3, 4]. The IL-6 is a pleiotropic cytokine secreted by T cells and macrophages. It is present in small amounts (<1-2 pg/mL), in body and concentration varies by time of day. Its level is elevated in inflammatory condition especially after surgery, trauma, infection, haematopoiesis, oncogenesis, immunoregulation [5]. It is capable of crossing the blood brain barrier and initiating synthesis of PGE₂ (ProstaglandinE₂) in the hypothalamus, thereby changing the body's temperature set point [6]; also it is released very early in an injury process [7]. Pre and post-operative administration of low dose steroid (Inj. Hydrocortisone 100mg) in patients undergoing TKR has shown to reduce the interleukin-6 level and its complications [8]. The hydrocortisone promotes lipolysis, Cyclic adenosine monophosphate induced breakdown of triglycerides, reduces production of acute phase reactants from macrophages and endothelial cells, negative regulation of Cyclooxygenases-2 and negative regulation of gene for cytokine in macrophages, endothelial cells and lymphocytes [9]. Thus steroid administration decreases the level of cytokines in the plasma and thus reduces the incidences of acute respiratory distress syndrome, Fat embolism syndrome, fever, and post-operative pain [8, 10]. So, the purpose of this study was to measure the changes in the level of Interleukin 6 after giving steroid in the patient undergoing TKA and thereby studying the reduction in complications.

Aims and Objectives

The purpose of this study was to observe the effect of intravenous hydrocortisone on cytokine Interleukin-6 (IL-6) as primary outcome and also to observe presence of Fever, Blood sugar level (BSL), Pain score (using Visual analogue scale), Range of motion (ROM) and SpO₂ (Saturation of oxygen) as a secondary outcome in the patients undergoing unilateral total knee arthroplasty.

Materials and Methods

This is a prospective randomized double blinded study of steroid modulation of cytokine (interleukin-6) release in 30 patients undergoing unilateral total knee replacement (TKR) surgery. All subjects gave their written informed consent for participation in the study before surgery. Adult patients undergoing primary, unilateral TKA were eligible for inclusion. Exclusion criteria included poorly controlled diabetes, current steroid therapy, smoking history, prior history of corticosteroid intolerance, Chronic liver disease and previous complications related to steroid use. Patients were divided into 2 groups. The study group received first dose of injection hydrocortisone 100mg I.V at the start of surgery followed by two more doses given eight hours apart while the control group received 100 ml of NS at similar intervals. All routine preoperative evaluation were done. Pre anaesthetic and physician check up were as per hospital guidelines. These guidelines were developed to eliminate patients considered to be at high risk for complications from total replacement surgery. Baseline assessment of individual patients for IL6 levels was done preoperatively 24hrs before the surgery followed by IL6 monitoring at 24hrs after surgery in both groups. Single surgeon performed all operations using standard midline skin incision and medial parapatellar arthrotomy. All patients received spinal anaesthesia. In all the cases pneumatic tourniquet used, which was inflated to 100 mm hg above the systolic blood pressure. Intravenous antibiotics (cephalosporin group) single dose was given pre operatively and continued for 48 hours post operatively. For post operative pain relief injection diclofenac, transdermal fentanyl patch were used for all the patient. Deep vein thrombosis prophylaxis was routinely provided with low molecular weight heparin and stockings. Temperature

charting, SpO₂ monitoring was done every 4 hourly till 48 hours post operatively. Patient were mobilized full weight bearing on the next day of surgery. Post operative blood sample were send for IL6 monitoring at 24hrs after surgery in both groups. Pain scoring of individual patients based on VAS (Visual analogue Scale) was done at 12 and 24 hours; Range of motion of the operated knee at 48 hours post operatively. Symptoms of deep vein thrombosis and pulmonary embolism were monitored throughout the postoperative period. Randomization was done using opaque envelopes containing labels inside marked with drug or placebo.

Observations and Results

Total 30 patients were included in the study. The study group included 8 males and 7 females, while the control group consisted of 7 males and 8 females. Mean age in study group was 65.6 years (59-74) and in control group it was 66.7 years (61-76). Mean BMI in both the groups were 30.4 kg/m² and 30.8 kg/m². Statistical analysis demonstrated no significant differences between groups for age and body mass index; so the two groups were considered to be appropriately matched on the main physical variables. In Study group, there were 4 patients with hypertension, 3 patients with diabetes mellitus, 2 patients with both diabetes and hypertension and 10 patients without any comorbidity illness. In Control group, there were 3 patients with hypertension, 3 patients with diabetes, 2 patient with both diabetes and hypertension and 11 patients without any co morbid illness. The associated co-morbid illness like diabetes mellitus and hypertension though anticipated to have some effect on the study didn't have any statistically significant influence. In both the groups average time duration of surgery was 80 min and average tourniquet time was 42 mins. In the study group average post operative BSL at 24 hours was 133.07 ±10.73 while in control group it was 121.60 ± 16.56 which is statistically significant (p-value< 0.05). In the study group 2 patients had fever, while in control group 7 patients had fever but statistically not significant (p-value > 0.05). Figure 1 demonstrates mean post operative SpO₂ at 4 hours interval upto 48 hours in both groups; it showed significant difference in the level of SpO₂ in first 24 hours (p-value < 0.05).

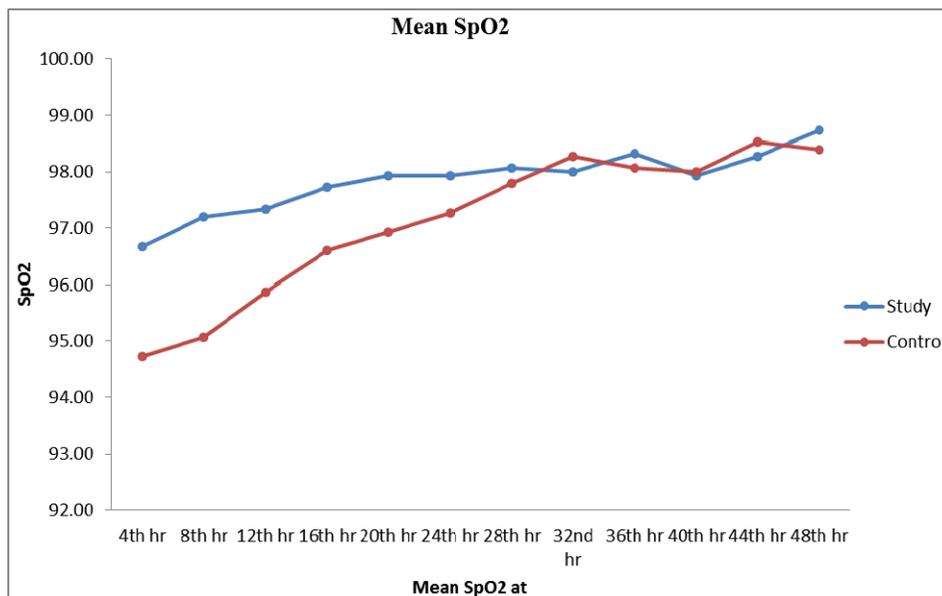


Fig 1

In study group average range of motion at 48 hours post operatively was 87.67 ± 7.53 while in control group it was 81.33 ± 9.54 , but statistically not significant ($p\text{-value} > 0.05$). Table 1 shows median IL 6 level at baseline and at 24 hours post operatively. There was significant difference in the level of IL 6 post operatively ($p\text{-value} < 0.001$).

Table 1

Median IL 6	Group		P-value
	Study (n=15)	Control (n= 15)	
At Baseline	7.11	7.16	0.999
at 24th hr	199.48	859	< 0.001

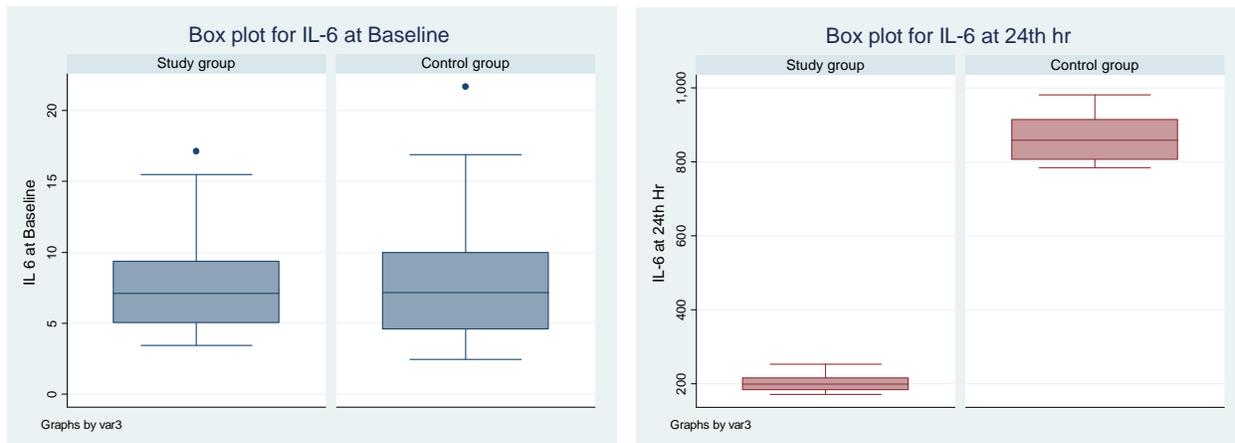


Fig 2

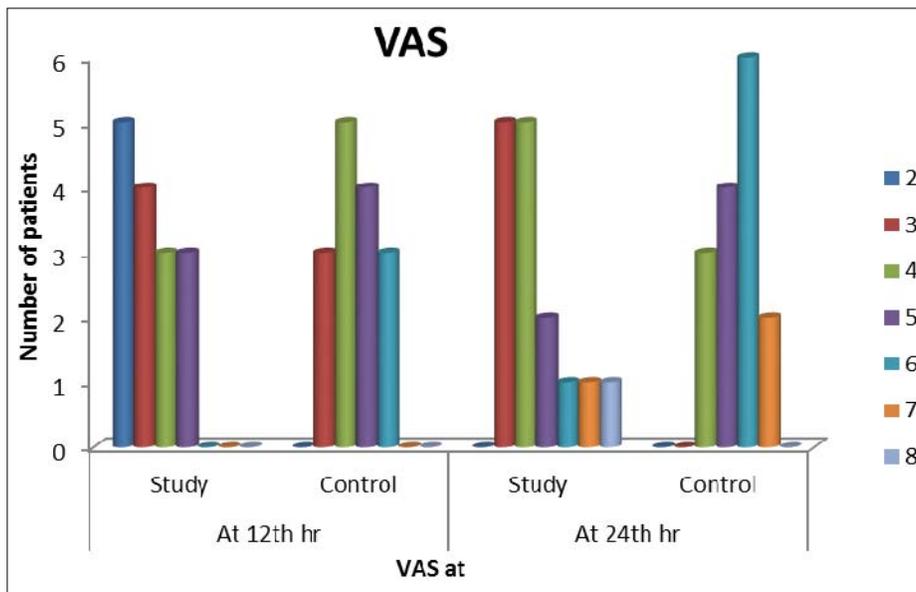


Fig 3: shows Visual Analogue Score (VAS) at 12 hours and 24 hours post operatively in both the groups.

Table 2: Shows mean Visual Analogue Score (VAS) at 12 hours and 24 hours post operatively in both the groups.

	Median VAS		P-value
	Study Group	Control Group	
At 12th hr	3	4	0.011
At 24th hr	4	6	0.019

By statistical analysis there was significant difference in mean VAS, $p\text{-value}$ at 12 hours 0.011 and at 24 hours 0.019.

Discussion

Bjornsson *et al.* [11] studied the process of inflammation which takes place after the major or elective surgery. They measured the level of cytokines like IL-1 β , IL-6, Tumor necrotic factor, IL-8,IL-10,IL-12. All these cytokines were pro inflammatory while IL-10 was anti-inflammatory. They concluded that only Interleukin-6 (IL-6) was significantly elevated from the

baseline. We studied 30 patients of unilateral total knee replacement in a prospective, randomized, double blind fashion. Out of 30 patients 15 patients in the study group received first dose of injection hydrocortisone 100mg I.V at the start of surgery followed by two more doses given eight hours apart while the control group received 100 ml of NS I.V at similar intervals. In the study done by Jules Elysee KM *et al*, Lipnitsky JY *et al.* [8] two doses of intravenous steroid were given which proved to be not effective in maintaining lower level of interleukin-6 (IL-6) beyond 24 hours. We evaluated the level of Interleukin-6 (IL-6) twice, first sample of blood was taken 24 hours before the surgery, second sample was taken at 24 hours after the surgery. In our study we found that, in the Study group average baseline IL-6 level was 7.11pg/ml and at 24 hrs it was 199.48pg/ml while in Control group baseline IL-6 level was 7.16pg/ml and at 24 hours it was 859pg/ml. Statistically there was significant difference

between median IL 6 score in both the group at 24th hours (p-value < 0.05). The corticosteroid may play physiological role in altering the immune response to the surgery. The addition of supplemental corticosteroid in our study may have boosted this natural process, which has lead to the greater suppression of IL-6 release. Similar results were seen in the study done by Kethy M. Jules-Elysee ^[10] *et al.* in which the levels of Interleukin-6 (IL-6) at 24 hours were 148.13±119.35pg/ml in the Study group while in the Control group it was 623.74±610.35pg/ml with the p-value =0.006. It is a well known fact that pulmonary complications are common after the major or elective surgeries. In a study done by Memtsoudis SG ^[12] *et al.* it was seen that despite younger age and lower co morbidity burden, procedure related complication and in hospital mortality were more frequent after bilateral Total knee arthroplasty versus unilateral knee arthroplasty (9.45% vs 7.07% and 0.03% vs 0.14%, P<0.0001), thus they concluded pulmonary complications were more in bilateral rather than the unilateral total knee replacement surgeries. In our study we have measured SpO₂ 4 hourly for 48 hours after the surgery in both control and study group and found significant difference between the mean SpO₂ (p-value < 0.05) at 4th hours to 24th hours postoperatively with better SpO₂ in study group, while from 24hours to 48 hours no significant difference was found among both groups. Clinically none of our patients developed signs and symptoms corresponding to fat embolism syndrome and acute respiratory distress syndrome. In the patient undergoing elective surgery Pain is of major concern which is produced due the local reaction at the site of surgical insult as described in a study by Caio Marcio Barros de Oliveira *et al.* ^[13]. In our study using the visual analogue scale (VAS) we have found that the median Visual analogue score (VAS) at 12 hours in Study group was 3 out of 10 while in Control group it was 4 out of 10, with the p-value of 0.011 while at 24 hours in Study group it was 4 out of 10 and in control group it was 6 out of 10 with the p-value of 0.019. Thus p-value of < 0.05 exists that means there is a significant difference between median pain score in study group and control group at 12th hours and 24th hours with better pain control in study group. In a study by Salerno ^[14] *et al.* similar results were found with reduction of pain postoperatively after giving short dose of corticosteroid regimens. We have compared knee Range of motion (ROM) of the patient at 48 hours postoperatively. In control group average range of motion was 81.33 ± 9.54 while in study group it was 87.67 ± 7.53. Statistically it was not significant (p-value>0.05), but proportion of the patients with better range of motion was higher in study group than control group. However in a study done by Kethy M. Jules-Elysee ^[10] *et al.* for bilateral total knee replacement they found a significant difference in ROM between both the group at the time of discharge (p-value 0.02). We have compared prevalence of fever in both group as the literature suggest that because the interleukin-6 (IL-6) is capable of crossing the blood brain barrier and can initiates the synthesis of prostaglandin (PGE₂) in hypothalamus thus changing body's temperature set point ^[6]. In the Study group 2 (13.33%) out of 15 had fever while in Control group 7 (46.67%) out of had fever; but statistically not significant (p-value > 0.05). In a study done by Kethy M. Jules-Elysee ^[10] *et al.* 8 (47.1%) out of 17 in control group while 2 (11.8%) out of 17 in study group had fever with significant p-value of 0.03, that means the correlation existed between occurrence of fever and elevated level of cytokines in their study. In our study though there is no statistical significant difference with

to occurrence of Fever, but the proportion of occurrence of Fever was higher in control group. In our study we have also compared blood glucose level preoperatively and post operatively in both group because there are evidences which suggest that the Blood sugar level (BSL) increases following surgical stress due to catecholamine (epinephrine) secretion following the activation of hypothalamo-pituitary axis ^[15, 16]. In the study group the average pre-operative BSL was 104.60 ± 12.22 while in the control group it was 100.80 ± 12.41. In the study group post operative BSL was 133.07 ± 10.73 while in control group it was 121.60 ± 16.56 with test p-value < 0.05 therefore rising trend was seen between mean BSL in both group post operatively, but it was not associated with any of its complications. Similar results were found in a previous study done by Kethy M. Jules-Elysee ^[10] *et al.* the average postoperative BSL in study group was 121.7±17.1 while in control group it was 104.4 ± 32.4 with p-value 0.07 which means that glucose levels were higher in the study group but only for first 24 hours.

Conclusion

In our study we conclude that a low dose of hydrocortisone given for a short period of over 24 hours perioperatively to the patients having unilateral total knee arthroplasty are associated with decreased level of inflammatory marker, the cytokine Interleukin-6 (IL-6). The lower levels of Interleukin-6 (IL-6) demonstrate less inflammation as a clinical effect of perioperative corticosteroid administration. The benefits included decrease pain scores measured by visual analogue scale, better saturation of oxygen (SpO₂) with no evidences of pulmonary dysfunction. Lower prevalence of fever was seen in study group than control which was not statistically significant, similarly prevalence of range of motion was better in study group than control group but not statistically significant, for that we would recommend further study with larger sample size needed to be done for definite conclusion. The blood sugar level has shown rising trends in some patients of study group than control group postoperatively with no associated complications for that blood sugar level monitoring should be done. Hence the small study and transient benefit warrant further larger studies regarding effects of perioperative corticosteroid on more long term outcomes.

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