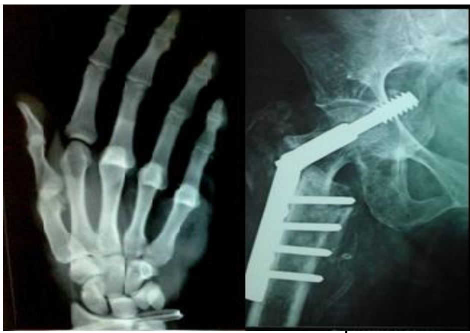

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To study the inflammatory markers in the perioperative period in total knee arthroplasty

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Abstract
Background: Osteoarthritis (OA) of knee is a degenerative disorder characterized by the softening, ulceration and focal loss of articular cartilage, sclerosis of the subchondral bone, marginal osteophyte formation and a range of morphological and biochemical changes in the synovium & capsule of the knee joint. Total knee arthroplasty (TKA) has been the treatment of choice for advanced osteoarthritis of knee. TKA is associated with significant post-operative pain. The aim of this study is an evaluation of inflammatory markers (ESR, CRP, INR, TLC) following TKA with use of tourniquet in the perioperative period.
Methods: Sample size (n=30) was taken A standard automatic pneumatic tourniquet was used during the surgery. Data on demographics, duration of surgery, Erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), Total leukocyte count (TLC), Coagulation profile (INR) and limb circumference were analysed. P-values < 0.05 are considered to be statistically significant. The entire data was statistically analysed using Statistical Package for Social Sciences (SPSS version 21.0, IBM Corporation, USA).
Results: The distribution of mean 6-hr post-op and 48-hr post-op ESR is significantly higher compared to mean pre-op ESR (P-value<0.001 for both). The mean% change at 48-hr post-op compared to pre-op in CRP is 1404.89% which was statistically significant. The change in preoperative INR versus postoperative 6th hr INR is not significant (P value>0.05) as well as the preoperative versus 48th hour. The mean% change at 48-hr post-op compared to pre-op in TLC is 96.24% with p value <0.001.
Conclusions: In this study it was found that there is a significant increase in inflammatory markers (ESR, CRP, TLC) in the post-operative period which is consistent with studies in the past. Due to small sample size of the study, the data generated can be utilized as a baseline to study correlation between pain and inflammatory marker levels on a larger scale at multicentric levels.

Keywords: Tourniquet, total knee arthroplasty (TKA), erythrocyte sedimentation rate (ESR), C reactive protein, total leukocyte count

Introduction

Osteoarthritis (OA) of knee is a degenerative disorder characterized by the softening, ulceration and focal loss of articular cartilage, sclerosis of the subchondral bone, marginal osteophyte formation and a range of morphological and biochemical changes in the synovium & capsule of the knee joint. It clinically presents with pain on activity and stiffness. When no known cause is found it is referred as primary OA of knee [1]. Osteoarthritis has been regarded as the 4th leading cause of disability worldwide [2]. Total knee arthroplasty (TKA) has been a successful surgical procedure for advanced arthritis of the knee. Knee replacements considerably relieve pain and restore function [3, 4]. Multiple authors report successful outcomes for 90% of patients even 15 to 20 years after surgery [5, 6]. Total knee arthroplasty (TKA) surgery can be associated with considerable postoperative pain [7]. The outcome of a successful knee replacement surgery depends on minimising soft tissue trauma; adequate postoperative pain relief to hasten recovery and hence reduced hospital stay & cost [8, 9]. A pneumatic tourniquet is commonly used in TKA surgery to improve surgical field visualisation and to decrease the operating time. The bloodless operating field also improves bone cement interface thus preventing component loosening in a cemented TKA. However, the use of tourniquet may result in more postoperative pain and may delay the recovery in comparison to a surgery done without tourniquet [10, 11]. This study was undertaken with an aim to study the levels of inflammatory markers in perioperative period.

Methods

30 cases of unilateral total knee arthroplasties conducted between November 2015 to September 2017 were considered for the study after fulfilling the inclusion & exclusion criteria. All the surgeries were performed by the senior surgeons. All the patients were given combined spinal-epidural anesthesia (12.5 mg bupivacaine 0.5%). Following this, the operative limb was exsanguinated and the tourniquet was inflated to 250 mm Hg and TKA performed. Patient demographics including age, sex, and body mass index; perioperative data including tourniquet time during surgery, the volume of fluid administered during 48 hr post-operative period was recorded. For thromboprophylaxis, all the patients were administered inj. LMWH (low molecular weight heparin) at a dose of 1mg/Kg body weight on the evening prior to surgery and then from the first postoperative day, morning daily doses were administered till discharge. The following parameters were recorded in each case: -age, sex, body mass index, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and total leucocyte count (TLC) as well as the change in INR preoperatively and then postoperatively at 6^{th} & 48^{th} hour.

Erythrocyte sedimentation rate (ESR) To observe the post-operative trend of inflammatory status, ESR values were recorded at the various point of time i.e. preoperative (baseline), postoperatively at 6^{th} and 48^{th} hour. As a response to inflammation, serum fibrinogen levels rise which enhances the erythrocytes to stick each other and hence stalk or rouleaux formation. Estimation of ESR was done with 2ml of venous blood using Westergren method. The rate of fall of RBC rouleaux was expressed as mm/hr. Normal reference values for an adult male is less than 20 mm/hr. and that for an adult female is less than 30 mm/hr.

C-reactive protein (CRP): CRP, being an acute phase reactant protein that is synthesized by liver as an early response to inflammation, quantitative CRP was also measured both at preoperative period and postoperatively at 6^{th} and 48^{th} hour. 1ml of the patient serum was subjected to immunoturbidometric assay in laboratory and result was expressed in mg/L. The normal reference range is less than 6mg/L. CRP rises rapidly, but nonspecifically in response to tissue injury and inflammation.

Total leucocyte count (TLC): As a surrogate marker of inflammation, to measure the post-operative inflammatory status total leucocyte count in whole blood can be measured. It was measured preoperatively and then at 6^{th} & 48^{th} hour postoperatively. 2 ml of blood was collected in EDTA vacutainer and the TLC was measured using autoanalyzer. The normal reference range is 4000 to 11000 per mm.

Prothrombin time (International normalized ratio) PT/INR- To observe the effect of limb preconditioning over the systemic coagulation profile, PT/INR was measured in each patient preoperatively a day before surgery and then postoperatively at 6^{th} hr & 48^{th} hr. The trend in INR was compared. 3 ml of blood was collected in a sodium citrate vacutainer. The analysis was done by a clot-based assay with automated coagulation analyzer. The normal reference range is 12+/-4 secs. The INR was derived from the formula: INR = (PT patient/PT normal) ^{ISI}, the ISI (international sensitivity index) as per the manufacturer of thromboplastin reagent used in the laboratory was 0.9. All the patients underwent same postoperative rehabilitation that consisted of knee range of motion exercises started in early postoperative period and walker assisted full weight bearing ambulation from the first postoperative day.

Inclusion criteria: Primary osteoarthritis of the knee

Exclusion criteria: primary osteoarthritis of Knee with severe deformities such as varus deformity more than 15 degree & fixed flexion deformity more than 20 degree, previous surgery on the affected knee, inflammatory arthritis of the knee, revision knee arthroplasty, previous history of injection of intra articular steroid or any viscosupplementation in the affected knee within six weeks of index total knee arthroplasty, immunocompromised patients, patients with peripheral vascular diseases in the affected limb, patients with deranged coagulation profile, patients operated under general anaesthesia, history of previous infection in knee.
All the patients were operated under spinal anaesthesia after cleaning, draping and tourniquet inflation by standard medial parapatellar approach. Implants from the same manufacture were used in all patients. Drain was used in all cases which was removed after 24 hrs.

Statistical methods: The data on categorical variables are shown as n (% of cases) and data on continuous variables are shown as mean ± standard deviation (SD) across all follow-ups. The intra-group pair-wise comparison of continuous variables is done using the paired t-test. The underlying normality assumption is confirmed before subjecting the study variables to t-test. In the entire study, the p-values less than 0.05 are considered to be statistically significant. All the hypotheses were formulated using two-tailed alternatives against each null hypothesis (hypothesis of no difference). The entire data is statistically analyzed using Statistical Package for Social Sciences (SPSS version 21.0, IBM Corporation, USA) for MS Windows

Results

A total of 30 patients were included in the study after fulfilling the above- mentioned inclusion and exclusion criteria. The demographic profile is as mentioned in Fig 1, 2. The distribution of mean 6-hr post-op and 48-hr post-op ESR is significantly higher compared to mean pre-op ESR (P-value<0.001 for both). The mean% change at 48-hr post-op compared to pre-op in ESR is 239.67%. Table 1. The distribution of mean 6-hr post-op and 48-hr post-op CRP is significantly higher compared to mean pre-op CRP (P-value<0.001 for both). The mean% change at 48-hr post-op compared to pre-op in CRP is 1404.89%. Table 2. The change in preoperative INR versus postoperative 6^{th} hr INR is not significant (P value>0.05) as well as the preoperative versus 48^{th} hour. Table 3. The distribution of mean 6-hr post-op and 48-hr Post-op TLC is significantly higher compared to mean pre-op TLC (P-value<0.001 for both). The mean% change at 48-hr post-op compared to pre-op in TLC is 96.24%. Fig 3.

Discussion

The total knee arthroplasty surgery itself possess significant surgical trauma to a patient, which in turn induces local as well as systemic inflammatory response. One of the major contributing factors for postoperative pain can be the post-operative swelling of the limb and degree of inflammation (95) [12]. The reperfusion injury after tourniquet deflation following a knee surgery may aggravate a local inflammatory reaction and hence pain (12, 97) [13, 14]. As evidenced by near-infrared monitoring and histological specimens, muscle damage appears about 30–60 min after inflating a tourniquet. There occurs a progressive decrease in pH (<6.5), decreased pO2, increased pCO2, increased potassium ion and increased lactate (35) [15]. However, these changes are usually mild and well tolerated. Tourniquet pain develops in up to two-thirds of patients, usually 30–60 min after cuff inflation. Tourniquet-induced hypertension occurs in 11–66% of cases. After deflation, the return of circulation leads to the development of the reperfusion injury (36) [16]. On release of the tourniquet, following reperfusion and oxygenation, reactive free radicals generate that cause endothelial dysfunction. This is also referred as the reperfusion injury (37) [17]. Deflation leads to a decrease in mean arterial blood pressure significantly, partly owing to the release of metabolites from the ischemic limb into the circulation and the decrease in peripheral vascular resistance. Transient increases in end-tidal carbon dioxide, decrease in temperature, and central venous oxygen tension are seen. There is an interaction between the activated neutrophils and the surface adhesion molecules on the vascular endothelium (38-40) [18, 20]. Leukocyte infiltration begins, and the expression of isolated neutrophils CD11b, CD18, endothelial cell adhesion molecule-1 (CAM-1) occurs. Venous embolization is another complication reported after deflation of tourniquet, especially of the lower limbs (41) [21]. It has been shown by Cheng *et al*. that free radicals generation increases mostly between 5-20 minutes following the release of the tourniquet after a total knee replacement (42) [22] This is particularly important in elderly patients undergoing knee replacement, for risk of perioperative cardiovascular and pulmonary complications (43) [23].

To observe the course of this inflammatory response in the early postoperative period we have measured the ESR, CRP and TLC levels both before and after surgery. The mean preoperative ESR level was 12.47 mm/hr with a standard deviation (SD) of 4.11; the 6^{th} hour postoperative rise was up to a mean level of 23.83 mm/hr (SD±6.60) with a rise up to a mean level of 39.03 mm/hr (SD±7.83). Similarly, the quantitative CRP values (in mg/dL) in our study preoperatively and postoperatively at 6^{th} and 48^{th} hour with mean±SD was 2.49 ± 1.26, 13.06±3.85 and 23.72±5.20 respectively. Various studies in past have tried to describe the perioperative variations in ESR following primary knee arthroplasty. In a Korean study with 108 primaries unilateral TKA Park *et al*. (97) [14] have found mean preoperative ESR to be 22.2mm/hr (SD ±12.14) which rose to 42.13 mm/hr (SD±37.37) at 2^{nd} postoperative day. The CRP values in mg/dL with mean±SD were 1.64±2.23 preoperatively which increased to 59.08± 35.42 on first postoperative day and 151.26± 54.34 on second post-operative day. In another study in Iran by Nazem *et al*. (98) [24] in 35 TKA patients found that the preoperative & 2^{nd} postoperative day ESR values (in mm/hr) with mean±SD were 19.1±12.9 and 75.33±28.1 and CRP values on preoperative vs postoperative day 1 & 2were 4.07±2.9 ,58.5±24.5 and 68.2±15.3 respectively. Both the above studies have followed up ESR and CRP levels for at least ninety days at various intervals and maximum values of ESR and CRP were noted on 5^{th} and 2^{nd} postoperative day respectively As the standard deviation in the data pool of the Korean study, Iranian study and our study are grossly different, a quantitative comment on percent change of preoperative and postoperative change of ESR and CRP cannot be derived with confidence. But, qualitatively, it may be mentioned that the fold wise rise in acute phase reactant like CRP in our study was less than the above two studies. (Table 3) Many studies in past have tried to report the trend of ESR and CRP levels after a joint arthroplasty, but most of them suggest limitations in studies for which it is difficult to interpret and find a conclusion. Some of them consider both total knee and total hip arthroplasties whereas some use very less sample size (99-104) [25, 30]. The levels of ESR and CRP in post-TKA patients reflect a measure of the acute inflammatory response after a surgical traumatic stimulus and can be used to monitor the course of the postoperative period after TKA since their levels rise rapidly, they have a comparatively shorter lag time and for their cost-effectiveness (110) [31]. Also as no evidence of infection occurred in all of our cases even after follow up, the increase in ESR and CRP can be interpreted as an indirect evidence of tissue damage during the arthroplasty surgery (111,112) [32, 33]. Previously, however, investigators have found additionally intraarticular levels of IL-6 (interleukin-6) & TNF-α (tumor necrosis factor-α) as useful markers to study inflammatory response following limb preconditioning in TKA patients (12) [13]. But given the ease of availability of ESR and CRP and their cost effectiveness we have tried to estimate their levels in our study population.

While observing the effect of limb preconditioning on postoperative increase in TLC count, we found that the levels of TLC in numbers per c mm with mean ±SD were 7383.33 ±2362.79, 11053.33 ±2382.22, 13470 ±2079.81 in preoperative,6^{th} hour and 48^{th} hour postoperative period respectively. The mean percent change at 48^{th} hour post-op as compared to pre-op levels in TLC was 96.24%. The incidence of preoperative leukocytosis (TLC >11000/cmm) was found in 6.67% of cases (2 out of 30), and that of the postoperative leukocytosis was found in 46.6% of cases (14 out of 30) in 6^{th} postoperative hour and was again raised to 90% of cases (27 out of 30) in 48^{th} postoperative hour. However, we have not followed up the leucocyte count beyond 48 hours. Deirmengian *et al.* (113) [34] in a retrospective study have concluded that leukocytosis is common after an arthroplasty surgery. The course of the rise of incidence of leukocytosis in their study followed a different trend in a larger sample size. The incidence of leukocytosis in preoperative period was 5.23% and that in postoperative day 1 & 2 was 20% and 31.5% respectively. However, in their study, they had included unilateral as well as bilateral total knee and hip arthroplasties. Hence, our data are in concurrence with the trend that rise in WBC count is an essential feature of normal response of systemic inflammatory process after a surgery (114) [35]. Another previous study by Hughes *et al*. (115) [36] who observed that the systemic inflammatory response is more with a total knee arthroplasty than a total hip arthroplasty and related the effect to tourniquet ischemia. This may explain the 90% incidence of leukocytosis at 48^{th} hour as compared to preoperatively 6.6% in our study population. In a randomized prospective study with 34 patients by Memtsoudis *et al*. (12) [13] the rise of inflammatory markers was significant following unilateral TKA. The surgical techniques, duration of tourniquet application during surgery, the extent of marrow debris and cement embolization following deflation of tourniquet are an independent predictor of systemic inflammatory response. In our study, with a tourniquet time of 88.57±8.26 minutes (mean ±SD), the increase in levels of inflammatory markers was modest.

While observing the change in coagulation profile we found that there was no significant change in PT/INR levels as compared to preoperative versus 6th hr postoperative or preoperative versus 48th hr postoperative levels. For the sake of thromboprophylaxis, we had administered inj. LMWH (low molecular weight heparin) at a dose of 1mg/Kg body weight to our patients on the evening prior to surgery and from the first postoperative day morning daily doses till hospitalization as per institutional protocol. None of our patients showed any clinical evidence of superficial or deep vein thrombosis. Memtsoudis *et al*. (93) [37] have not found any significant change in coagulation profile in preconditioning group vs control group while measuring prothrombin fragments, D-dimer, and thrombin-antithrombin complex.

Limitations of the study: The study has many limitations including a small sample size for which extrapolation of the result into a general population is difficult. Therefore, a larger population-based prospective randomized comparative study may be designed to elaborate the effects of ischemic preconditioning in TKA surgery to derive a firm conclusion.

Conclusion

The postoperative pain control in a total knee arthroplasty (TKA) surgery has been a challenge for the orthopedic surgeon. In spite of the intervention of multimodal analgesia, a combined approach of using a non-pharmacological and non-invasive method with other pharmacological agents is still evolving. To conclude, proper patient selection and proper counseling prior to a knee arthroplasty surgery is important to achieve a long-term patient satisfaction. In spite of the shortcoming of our study, the fact that the literature is lacking enough studies regarding the utility of limb preconditioning in TKA, the data generated out of our study population can be used for conducting further multicenter trials in future.

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Declarations

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Conflict of interest: None
Ethical approval: Approval of institutional ethical committee taken.

Table 1: The comparison of pre-op (Preoperative) and post-op (Postoperative) ESR

	ESR (n=30)	
Follow-up	**Mean**	**SD**
Pre-op	12.47	4.11
6-hr Post-op	23.83	6.60
48-hr Post-op	39.03	7.83
% Change At 48-hr Post-op	239.67%	--
P-value (Pair-wise)		
Pre-op v 6-hr Post-op	0.001^{***}	
Pre-op v 48-hr Post-op	0.001^{***}	

Table 2: The comparison of pre-op (preoperative) and post-op (postoperative) C - reactive protein (CRP)

	C-Reactive Protein (CRP) (n=30)	
Follow-up	**Mean**	**SD**
Pre-op	2.49	1.26
6-hr Post-op	13.06	3.85
48-hr Post-op	23.72	5.20
% Change At 48-hr Post-op	1404.89%	--
P-value (Pair-wise)		
Pre-op v 6-hr Post-op	0.001^{***}	
Pre-op v 48-hr Post-op	0.001^{***}	

Values are Mean and Standard Deviation (SD). P-values by Paired t test. P-value<0.05 is considered to be statistically significant. *P-value<0.05, **P-value<0.01, ***P-value<0.001, NS-Statistically Non-Significant.

Table 3: The comparison of pre-op (preoperative) and post-op (postoperative) INR (International Normalized Ratio)

	Prothrombin Time INR (n=30)	
Follow-up	**Mean**	**SD**
Pre-op	1.32	0.248
6-hr Post-op	1.38	0.20
48-hr Post-op	1.34	0.20
P-value (Pair-wise)		
Pre-op v 6-hr Post-op	0.219^{NS}	
Pre-op v 48-hr Post-op	0.728^{NS}	

Table 4: Comparing the fold-wise increase in mean in ESR and CRP among studies

Studies	ESR			CRP		
	Pre-operative period	**48th hr. post-operative period**	**Fold wise increase in mean**	**Pre-operative period**	**48th hr. Post-operative period**	**Fold wise increase in mean**
Korean study(n=108)	22.2±12.14	42.13±37.37	1.89	1.64±2.23	151.26±54.34	92.23
Iranian study (n=35)	19.1±12.9	75.33±28.1	3.94	4.07±2.9	68.2±15.3	16.75
Our study (n=30)	12.47±4.11	39.03±7.83	3.12	2.49±1.26	23.72±5.20	9.52

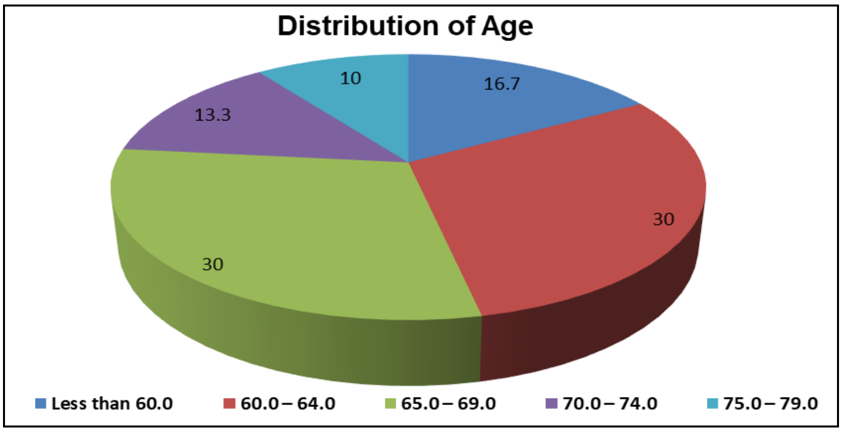

Fig 1: Age Distribution of patients

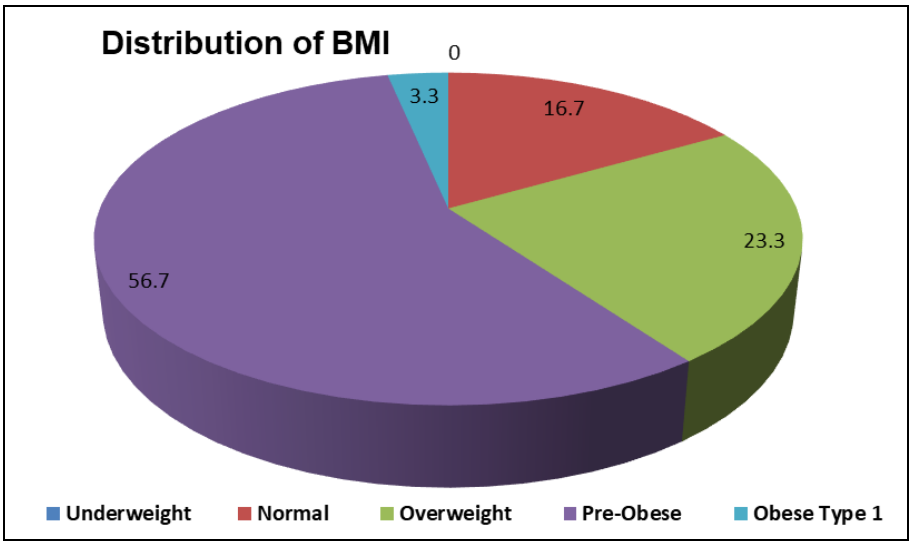

Fig 2: Distribution of BMI of patients

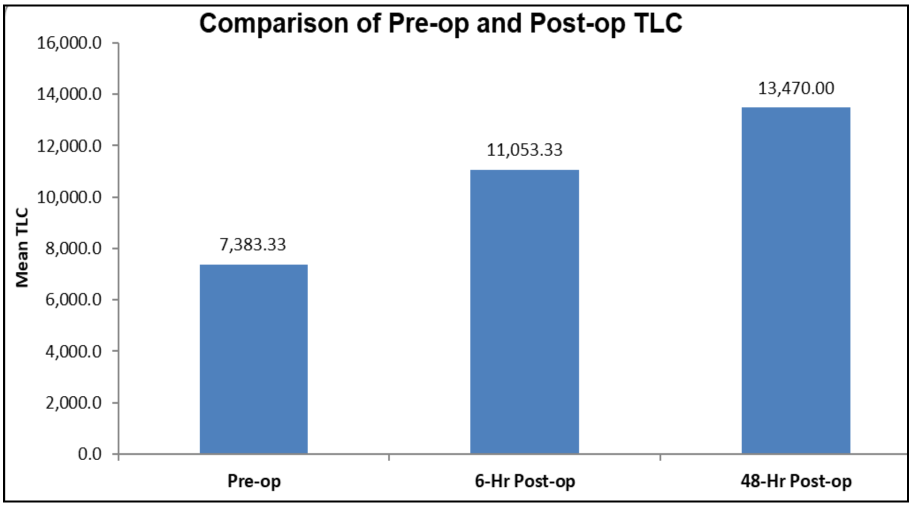

Fig 3: Comparison of Pre and Post operative Total Leukocyte count

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