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**TOTAL KNEE ARTHROPLASTY: ARE SOUTH INDIAN FEMALES AT HIGH RISK
OF TOTAL KNEE REPLACEMENT WITH INCREASE IN AGE?**

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ABSTRACT

Objective: To study the factors contributing to total knee replacement. **Methodology:** Pharmacoepidemiological study on 150 patients was conducted who underwent TKA and THA over a period of 6 months. Patient's information was collected from the case records and the data was compiled and subjected to analysis for prescribing pattern and drug - drug interactions. Rationality of the prescription was evaluated using WHO core indicators and NLEM. **Results:** Female population (71%) contributed to more knee and hip replacement surgeries compared to male (29%). Age group between 60-70 years had higher surgeries compared to the other age groups. Class 1 obesity with the BMI ranging from 30-40 (45%) had more surgeries followed by overweight group (39%). 89% of the population has total knee replacement surgery where as a smaller population had undergone total hip replacement. A total of 2701 drugs were utilized for post surgical management. Nutritional supplements (31.2%) contributed to the major proportion of the drug prescribed. Analgesics (14.2%), steroids (12.2%), Anti-ulcer (11.1%), anticoagulants (6.14%), antihistamines (6%), CNS agents (5.84%), laxatives (5.8%), antibiotics (5.5%) and bisphosphonates (1.5%) were also found in the prescription. According to WHO prescribing indicators, the average number of drugs prescribed per prescription was 18, drugs prescribed by generic name contributed to (12.8%), antibiotic per prescription (5.3%), injections per prescription (28.8%) and NLEM drugs per prescription (62.8%) were found. Out of 150 prescriptions 186 drug - drug interactions were found, among them 62.9% were severe, 33.3% moderate and 3.7% minor drug - drug interaction. Diclofenac + Rivaroxaban ranked first among DDIs. **Conclusion:** Females above the age of 60 and are obese are at high risk of knee replacement surgeries. Multidrug therapy has leads to drug - drug interactions and might potentially harm the patient.

KEYWORDS

Knee replacement surgeries, Arthroplasty, Drug - drug interactions and WHO prescribing indicators.

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INTRODUCTION

Joint arthroplasty is a major advance in the treatment of chronic refractory pain. It is indicated in patients for whom conservative medical therapy has failed¹. Total knee arthroplasty (TKA) and Total hip arthroplasty (THA) are the most common and successful surgical interventions performed annually to treat pain in the affected joint and with

the aging population, the number of arthroplasty conducted each year is projected to increase at a staggering rate².

Arthroplasty surgery (e.g: Total knee replacement (TKR), Total hip replacement (THR) typically restores function and provides pain relief and improved quality of life in patients with Osteoarthritis (OA). These procedures are usually reserved, for patients with functional impairment in whom exercise, weight loss, activity modification and physical therapy are no longer effective³.

Total Knee Arthroplasty [TKA]

TKR is a surgical procedure in which an artificial joint or prosthesis replaces a damaged joint. The need for TKR is primarily pain and limited functioning. Daily activity must be substantially affected by pain, followed by functional limitations to be considered a candidate for TKR.

There are 3 different types of knee prostheses. Non constrained prostheses use the patient's ligaments and muscles to provide the stability of the prosthesis. Semi-constrained prosthesis provides some stability for the knee and do not rely entirely on the patients ligaments and muscles to provide the stability. Constrained prosthesis is for patients whose ligaments and muscles are not able to provide the stability for the knee prosthesis.

Non-cemented process involves the use of prosthesis with a rough porous surface that is designed in a way it can let the bone grow into it, which eliminates the need for cement in the procedure. The prosthesis is fitted and fixed next to the bone with metal pegs and screws. The bone grows and fixes to the knee replacement prosthesis. Recovery time is longer to walk compared to using cemented prostheses. Advantage of this procedure is that if the prosthesis does loosen over time, there is a less bone loss due to the lack of the irritant cement.

Hybrid fixation is a combination of cemented and non-cemented procedures. In this process the femur is cemented, the tibia is not cemented. In hybrid fixation and non-cemented procedures, the long-term outcomes are not much known due to the recent advancement in these technologies. Most

knee replacement surgeries use the cemented procedure.

Total Hip Arthroplasty [THA]

Total hip arthroplasty is an orthopedic procedure in which the diseased cartilage and the bone of the femoral head and the acetabulum is replaced with an artificial ball joint, which includes a stem inserted in to the femur with a ball on the top and an artificial acetabular socket with a liner inside. These three parts are referred to as the prosthesis or arthroplasty. To yield successful results, these total hip arthroplasty components must be fixed firmly to the bone, either with polymethylmethacrylate cement or in more recent uncemented designs, by bony ingrowths into a porous coating in to the implant, resulting in "biologic fixation". Revision total hip arthroplasty is carried out in patients where there is failure of a previously implanted prosthesis⁴.

METHODOLOGY

Retrospective study was carried out in a tertiary care multispecialty hospital, Chennai, during January 2019 to June 2019 and was approved by hospital research committee. All patients's undergone total knee and hip arthroplasty in orthopedic department, above the age of 40 were taken for the study. Patients with co morbidities like DM, HTN, CAD and Asthma were included. Patients who had previous history of knee or hip replacement (revision TKA and THA), Road traffic accident cases, critically-ill patients, patients with high blood sugar levels (HbA1c > 7.5), patients case with incomplete information were excluded from the study.

Information like, Socio demographic details, Clinical diagnosis, Clinical manifestations, Local examination findings, Laboratory data like hematological profile, coagulation profile, Biochemistry, Renal function test, X-ray and other parameters were collected. Drug data included brand name, generic name and dose route of administration, frequency and duration of treatment was obtained from the treatment chart.

A total of 161 cases were collected and 11 prescriptions were excluded due to insufficient data and the remaining 150 cases were considered for analysis.

Statistical Analysis

Age, gender, local examination, clinical diagnosis, co-morbid conditions, investigations carried out, drugs prescribed and drug-drug interactions was analyzed by using descriptive statistical analysis, mean \pm SD were calculated using SPSS version 24.

RESULTS

Out of 150 patients 71% were female, 29% were male. Most of the patients were above 60 years (53%) years who underwent replacement surgery. Body Mass Index was calculated based on the height and weight. 45% of the population belongs to class I obesity (BMI 40 to 50) and 39% belongs to overweight group (BMI 30-40).

Out of 150 surgeries considered for the study, 134 patients had Total Knee Replacement (89%) of which majority was bilateral knee replacement and 16 patients had Total Hip Replacement (11%) surgery.

Most of the patients had knee pain, swelling at the joints and difficulty in walking. A total of 2701 drugs were prescribed to these patients. Majority of the drugs prescribed were nutritional supplements 31%, followed by analgesics 14%, steroids 12%, anti-ulcer 11%, anticoagulants 6%, antihistamines 6%, CNS agents 6%, laxatives 6%, antibiotics 6% and bisphosphonates 2%.

Cefuroxime (89%) was prescribed more for surgical prophylaxis. Opiate + NSAIDs were mostly prescribed (90%) analgesics to manage post operative pain. To manage arthritis Paracetamol (15%), Diclofenac + Etoricoxib (11%) and Ketorolac + Paracetamol (9%) were used. Anti-anxiety drugs were also prescribed to calm down the patients (83%); sedative (3%) and antidepressants (3%) were prescribed to a few patients. Vitamin D₃ (16%), Vitamin C (16%), Enzymes (16%), Vitamin E (16%) were equally found in most of the prescriptions as supplements.

To analyses the prescribing pattern of drugs, WHO Prescribing indicators were used in the study, accordingly: drugs prescribed by generic name was 393 (14.5%), number of antibiotics prescribed was 164 (6.07%), number of injections prescribed was 1611 (32.5%) and number of drugs prescribed from NLEM was 879 (59.6%).

Out of 186 drug - drug interactions, 117 (62.9%) were found to be severe drug - drug interactions, 62 (33.3%) were found to be moderate drug - drug interactions, 7 (3.7%) were found to be mild drug - drug interactions.

DISCUSSION AND CONCLUSION

A retrospective study was conducted amongst south Indian population who had knee, hip replacement surgery during the year 2017 to 2018. 150 knee and hip replacement surgeries were selected for the study that had the appropriate study criteria's and fit into the inclusion list.

From the present study we observed that TKA and THA prevalence is high above age 60 and low in age group of 40-50 years of age. Quintana J M *et al*⁶ had a similar report that TKA and THA were more common in 60-69 years of age group followed by the age group 70-79 years.

In our study, demographic profile showed that TKA and THA were common in females (70.6%) than males (29.3%). The difference may be because females in their post menopause period have low estrogen which may leads to high risk of developing osteoarthritis, a predisposing factor for THA and TKA. This can also be due to small joints in women and lesser absolute amount of cartilage. Quintana JM *et al*⁶ also showed same results.

Obesity and overweight have long been recognized as potent risk factor for OA especially of the knee it reflects in our study. There is a strong relationship between obesity (measured by BMI) and total hip and knee replacement surgeries as a measure of OA. Patients belonging to class 1 obesity (BMI 30kg/m² to 40kg/m² (44.6%) and overweight (BMI- 25kg/m² to 29.9kg/m² (38.6%) showed high prevalence to TKA and THA when compared to patients of normal weight (BMI- 18.5kg/m² to 24.9kg/m²).

Studies conducted by Wendeböe A. M *et al*⁷ also concluded the same.

In our study signs and symptoms like pain and walking difficulty (KOA=45.5%, HOA=62.5%) was found to be more in OA. In addition to pain and walking difficulty, swelling (KOA=40.29%, HOA=12.5%) was also found to be a chief complaint in OA. Gurang S *et al*⁸ also concluded the same.

Among various joints involved in OA, knee joint was most commonly affected and most patients underwent TKR (89.3%). In TKR majority of the patients underwent bilateral TKR (61.94%) followed by right TKR (20.1%). When compared to TKR (89.3%) the patients who underwent THR (10.6%) was found to be very less. Around 14 patients underwent THR in our study of which 7 patients (43.7%) had with bilateral THR. Berger A *et al*² also concluded the same.

Osteoarthritis without co-morbid conditions was found to be 22% and with co-morbid conditions was found to be 78%. The most common co-morbid conditions with OA were cardiovascular and endocrine disease. Hypertension and DM was frequently present. In addition many female patients were found to have hypothyroidism, in our study. Jansen E *et al*⁹ also concluded the same.

For 150 patients, 2701 drugs were used for the therapeutic management after the surgical procedure. Majority of the drugs prescribed in the study was nutritional supplements (31.2%) followed by analgesics (14.2%), steroids (12.2%), Anti-ulcer (11.1%), anticoagulants (6.14%), antihistamines (6%), CNS agents (5.84%), laxatives (5.8%), antibiotics (5.5%) and bisphosphonates (1.5%). In a similar study conducted by Berger A *et al*² showed that analgesics utilization was greater.

In the present study, cephalosporin (cefuroxime-89.3%) was intensively prescribed prophylactic antibiotic for knee and hip arthroplasty. This may be because of cephalosporin have a good safety profile, a long half-life and good penetration in bone, synovium and muscle. The monotherapy of cephalosporin were prescribed more than fixed dose combination. The fixed dose combination

cefoperazone+sulbactam (8%) were used least. The results were similar to study conducted by Meehan J *et al*¹⁰.

In the present study opiate + NSAIDs were given in combination for majority of the patients (90%) and NSAIDs alone were used for (4.66%). Combination of the NSAIDs alone without opiates was given for (3.33%). This indicates that combined use of systemic opioids and NSAIDs relieved postoperative pain more effectively than single-drug regimen. Among the NSAIDs monotherapy paracetamol was prescribed mostly (14.6%) followed by diclofenac (2.6%) ketorolac (2%) and etoricoxib (2%). In combination therapy, combination of (diclofenac + paracetamol + etoricoxib) mostly prescribed (42%) and combination of (ketorolac+diclofenac+etoricoxib) was least prescribed (3.3%). This result was similar to study conducted by Jin F *et al*¹¹.

Clinical guidelines recommend pharmacological prophylaxis for patients undergoing total knee and hip arthroplasty for at least 10 days after the surgery. In our study new oral anticoagulants rivaroxaban (68.6%) was mostly prescribed, followed by apixaban (13.3%). There were no reported complication like bleeding and VTE occurrence associated with these new oral anticoagulants (factor Xa inhibitors). This suggest that factor Xa inhibitors was significantly more effective than other anticoagulants in TKA and THA. This result was similar to study conducted by Friedman JR *et al*¹².

In our study, steroids were prescribed for all the 150 patients. Most patients received corticosteroids monotherapy (57.3%) when compared to combination of corticosteroids and anabolic steroids nandrolone decanoate (42.7%). In the corticosteroids utilization, most patients received combination of hydrocortisone+methyl prednisolone (72%) than the single drug regimen. This result were similar to study conducted by Li D *et al*¹³ and Hohmann *et al*¹⁴.

NSAIDs are often co-administered with anti-ulcer drugs to reduce NSAID-induced gastrointestinal adverse events. In the present study PPI +

Mucoprotectant (sucralfate) (91.3%) were mostly prescribed to prevent GI bleeding/ulcer associated with NSAIDs and anticoagulants. Similar study was conducted by Gwee A. K *et al*¹⁵.

Antianxiety drugs were majorly used to reduce the anxiety of the patients, followed by the drugs to overcome depression and to calm the patients. Buvanendran A *et al*¹⁶ also concluded the same.

In the present study, all 150 patients were prescribed with nutritional supplements. Among them vitamin C (16.3%) was comparatively prescribed more than Enzictra DS (trypsin + bromelain + rutoside + papain) (15.9%), Evion LC (vitamin E+levocarnitine) (15.8%), vitamin D₃ (15.7%) and multivitamin (15.1%). A similar study conducted by Berend K R *et al*¹⁷ also concluded the importance of vitamins and minerals after TKA and THA.

In the present study, we categorized the prescribed drugs according to WHO prescribing indicators. Average number of drugs per prescription was found to be 18. WHO prescribing standard of average number of drugs per prescription are 1.6 - 1.8. This shows that average number of drugs per prescription in this study is much more than that of WHO standards for the drugs per prescriptions.

Average percentage of drugs prescribed by brand name (85.5%) is more than that of prescribed by generic name (14.5%). WHO prescribing indicators standard of percentage of drugs per prescription is 100%. This shows that average percentage of generic drugs per prescription in this study is much less than the WHO standard of the generic drugs per prescription, which is similar to the study conducted by Chaudhary M K *et al*¹⁸. Practice of using more branded drugs and lesser generic drugs had been observed in the study, this needs to be changed for the benefit of the patients.

Average percentage of antibiotics per prescription is 6.07%. WHO prescribing indicators standard of percentage of antibiotics per prescription is 20 - 26.8%. This shows that average percentage of antibiotics per prescription in this study is less than the WHO standard of the antibiotics per

prescription. Average percentage of injections per prescription is 32.5%. WHO prescribing indicators standard of percentage of injections per prescription is 13.4-24.1%. This shows that the average percentage of injections per prescription in the study is higher than the WHO standard of the injections per prescription.

Average percentage of NLEM drugs per prescription is 59.64%. WHO prescribing indicators standard of percentage of NLEM drugs per prescription are 100%. This shows that average percentage of NLEM drugs per prescription in this study is less than the WHO standard of the NLEM drugs per prescription. This corresponds to the results reported by Chaudhary M K *et al*¹⁸ it suggests poor adherence to WHO prescribing indicators in the present study.

Drug interactions occur when two or more drugs react with each other. Sometimes drug interactions may cause unexpected side effects. All the 150 prescriptions are found with drug -drug interactions. Many prescriptions found with DDI because of co morbid conditions. 150 prescriptions were analyzed and 186 drug - drug interactions were identified. 62.9% of the interaction was severe, 33.3% moderate and 3.7% minor drug - drug interactions, this is in contrast to that found in another report Jhaveri B N *et al*¹⁹.

Our study found that the average number of drug - drug interactions increased as the number of drugs in the prescription increased. This finding was similar to the another published report were the potential for a DDI increased from 13 - 82% as the number of medications increased from 2 to 7 or more. In the present study number of drug interaction are more because the average number of drugs prescribed per prescription is (18) more.

Table No.1: Factors affecting decision to perform THA AND TKA⁵

Age and co morbid factors	Age >80 years
	Age <50 years
	Co morbidity
	Alcohol abuse
	Weight>200 lb
Physical factors	History of deep vein thrombosis
	Leg varicosities
	Arterial insufficiency of legs
	Neurological disease of hip/knee
	Severe bone mass
	Poor soft tissue coverage
	Poor hip/knee musculature
Psychological factors	Chronic depression, Dementia
	Poor motivation, Limited cooperation
	Patient wants psychological benefits
	Hostile personality
	Return to work, Be independent
Functional and legal factors	Return to sports
	Unrealistic expectations
	Limited home care, Pending court case.

Table No.2: Chief complaints of patients KOA (n -134) HOA (n=16)

S.No	Diagnosis	Category	Complaints	Frequency	Percentage (%)
1	KOA (n=134)	1	KP+WD	61	45.5
		2	KP+WD+WS	10	7.46
		3	KP+Sw+WD	54	40.29
		4	KP+Sw+WD+WS	9	6.71
2	HOA (n=16)	5	HP+WD	10	62.5
		6	HP+Sw+WD	4	25
		7	HP+Sw+WD+WS	2	12.5

KP - Knee Pain, HP - Hip Pain, WD - Walking Difficulty, WS - Walking with support, Sw Swelling

Table No.3: Total drug utilization (n=2701)

S.No	Category	Frequency	Percentage (%)
1	Antibiotics	150	5.5
2	Analgesics	385	14.2
3	Anticoagulants	166	6.14
4	Steroids	332	12.2
5	Anti - ulcer	300	11.1
6	Antihistamines	164	6
7	CNS agents	158	5.84
8	Biphosphonates	42	1.5
9	Nutritional supplements	845	31.2
10	Laxatives	159	5.8

Table No.4: Antibiotics prophylaxis (n=150)

S.No	Antibiotic	No of patients (n=150)	Percentage (%)
1	Cefuroxime	134	89.33
2	Cefoprim	3	2
3	Cefaperazone + Sulbactum	12	8
4	Meropenam	1	0.66

Table No.5: Class of analgesics (n=150)

S.No	Class	Number of Patients (n=150)	Percentage (%)
1	Opiate + NSAIDs	135	90
2	NSAIDs + NDAIDs	7	4.66
3	NSAIDs + Enzymes	5	3.33
4	Opiate + NSAIDs + Enzymes	3	2

Table No.6: NSAIDs utilization (n=150)

S.No	NSAIDS	No of patients (n=150)	Percentage (%)
1	Ketorolac	3	2
2	Diclofenac	4	2.6
3	Etoricoxib	3	2
4	Paracetamol	22	14.6
5	Ketorolac + Diclofenac	2	1.3
6	Ketoralac + Etoricoxib	3	2
7	Ketorolac + Paracetamol	14	9.3
8	Diclofenac + Etoricoxib	16	10.6
9	Diclofenac + Paracetamol	5	3.3
10	Etoricoxib + Paracetamol	8	5.3
11	Ketorolac + Diclofenac + Paracetamol	8	5.3
12	Ketorolac + Diclofenac + Etoricoxib	5	3.3
13	Diclofenac + Paracetamol+ Etoricoxib	42	28
14	Ketorolac + Diclofenac + Etoricoxib + Paracetamol	15	10

Table No.7: Nutritional supplements utilization (n=845)

S.No	Supplements	No of supplement (n=845)	Percentage (%)
1	Vitamin B ₁	8	0.94
2	Vitamin C	138	16.3
3	Vitamin D ₃	133	15.7
4	Evion LC (vitamin E + levocarnitine)	134	15.8
5	Multivitamin	128	15.1
6	Coenzyme Q10	102	12
7	Calcium	38	4.5
8	Livogen	12	1.4
9	Probiotics	17	2
10	Enzictra DS (trypsin + bromelain + rutoside + papain)	135	15.9

Table No.8: WHO Prescribing indicators categorization (n=2701)

S.No	Indicators	Frequency	% out of total drug prescribed	WHO prescribing
1	No. of drug prescribed by generic name	393	14.55	100
2	No of antibiotic prescribed	164	6.07	20-26.8
3	No of injections prescribed	1611	32.54	13.4-24.1
4	No of drug prescribed from NLEM	879	59.64	100

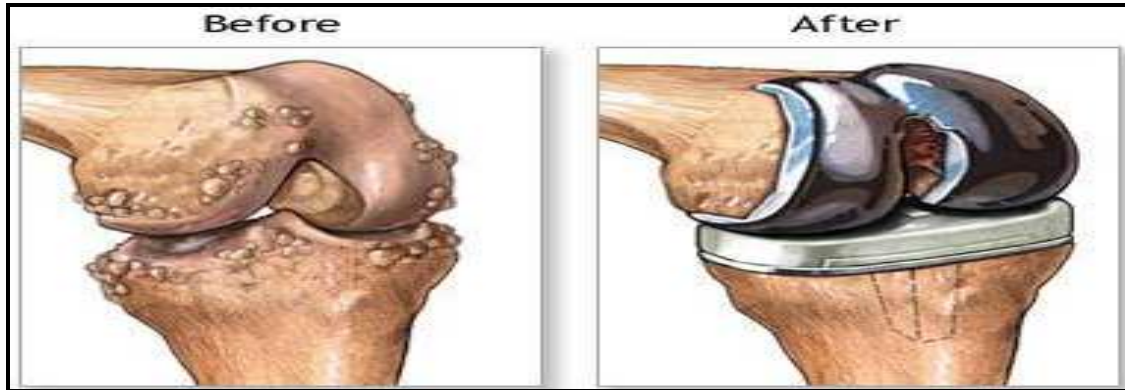


Figure No.1: Osteoarthritis of the knee and arthroplasty

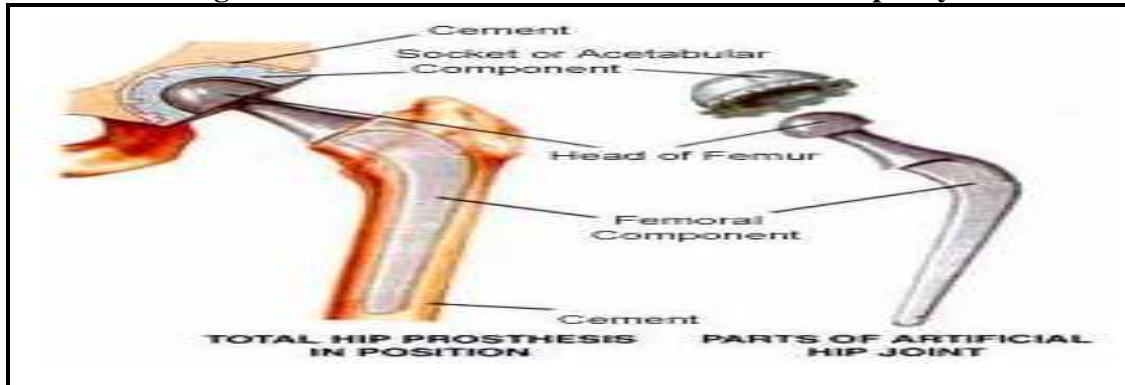


Figure No.2: Prosthesis of Total Hip Arthroplasty

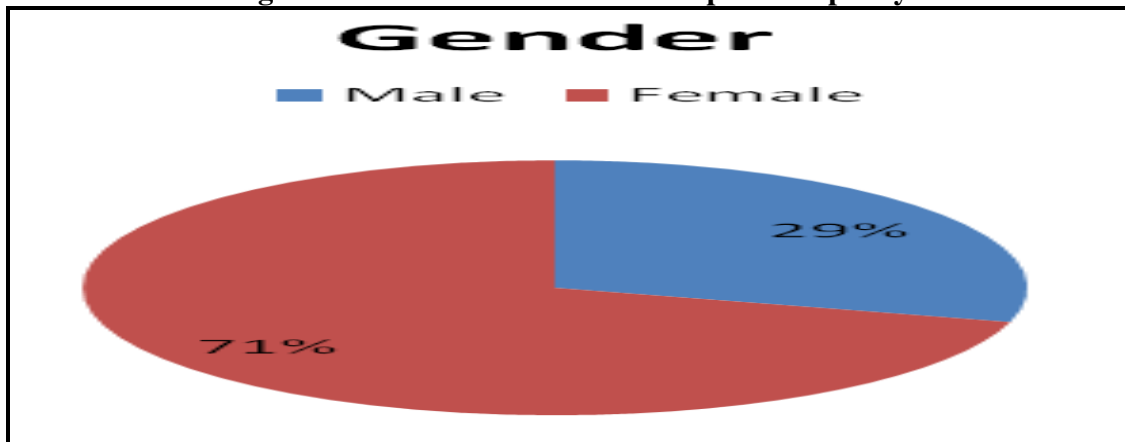


Figure No.3: Gender distribution

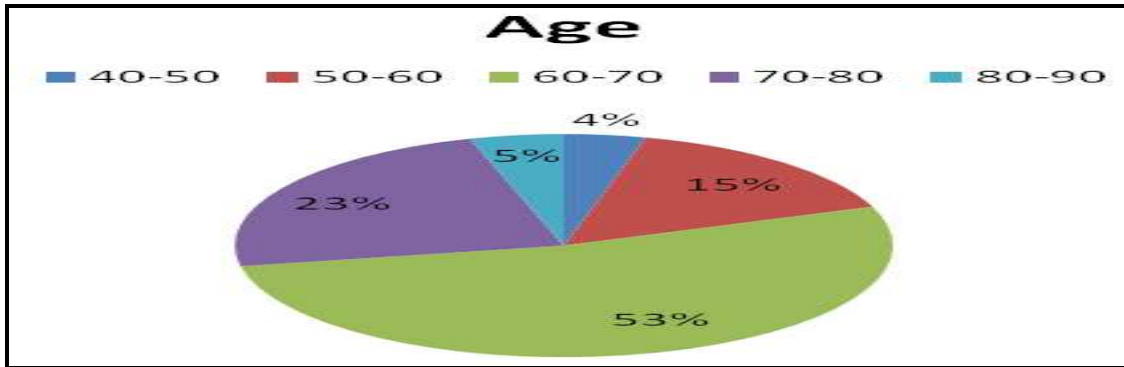


Figure No.4: Age distribution

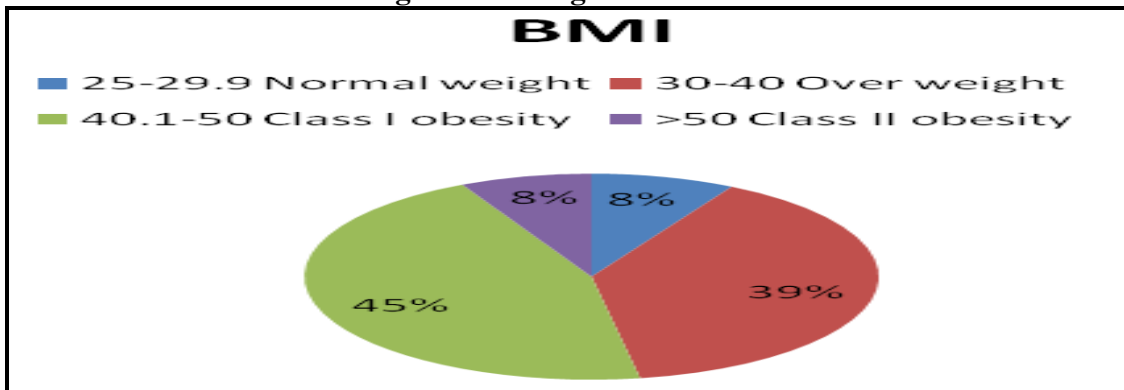


Figure No.5: BMI

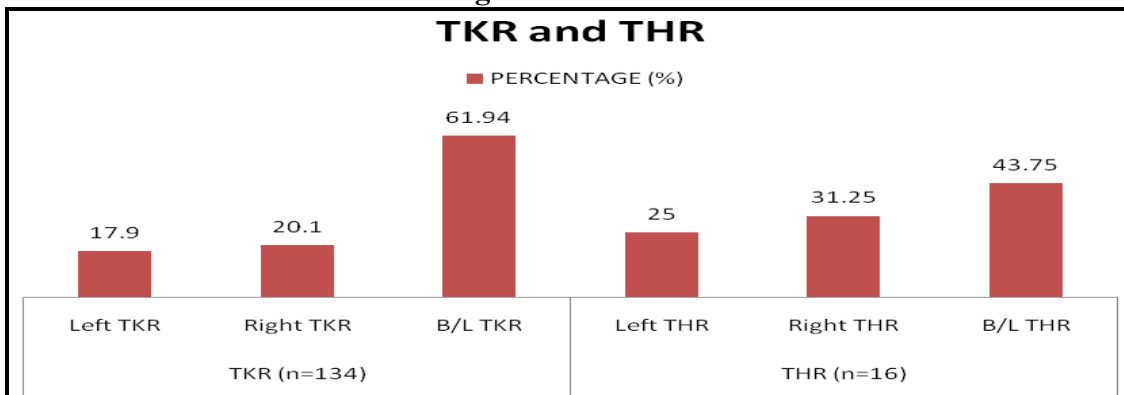


Figure No.6: Type of TKR/THR surgery

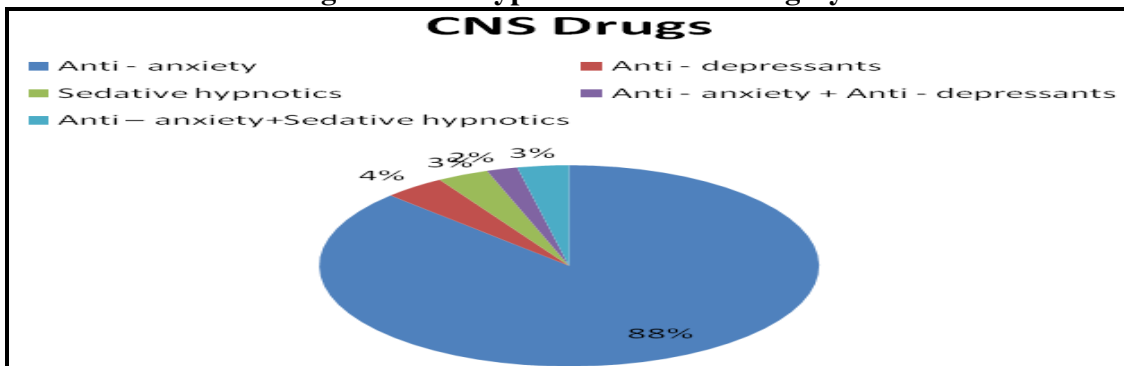


Figure No.7: CNS drug utilisation

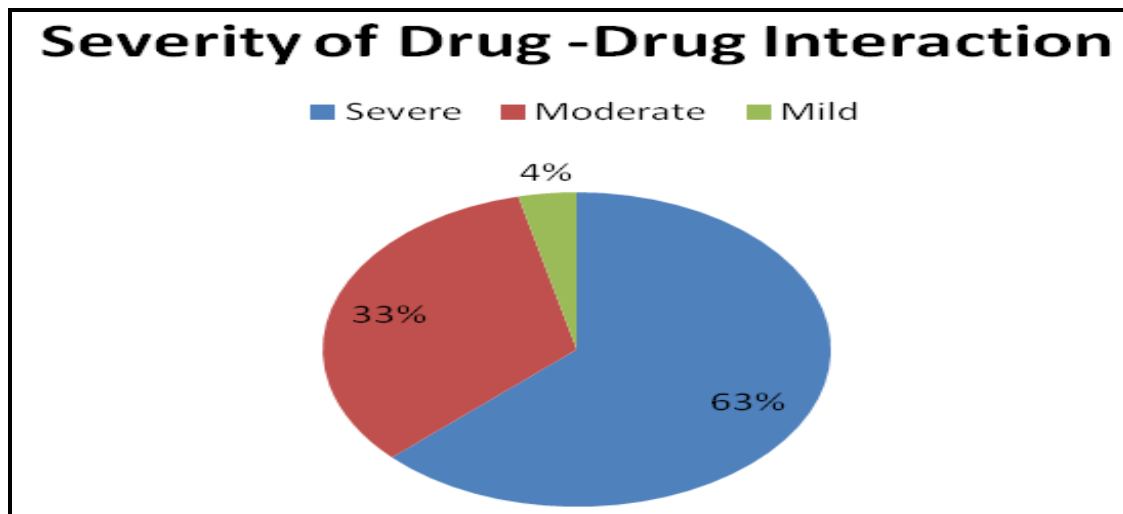


Figure No.8: Severity of drug interaction

CONCLUSION

Treatment after TKR and THR involves multi-drug therapy which includes antibiotics, analgesics, anticoagulants, steroids, antihistamines, anxiolytics, bisphosphonates and nutritional supplements. New oral anticoagulants like rivaroxaban were used more than the traditional anticoagulants such as heparin and warfarin. Vitamins and minerals especially vitamin C, vitamin D₃, vitamin E, Coenzyme Q10 and oral enzymes plays an important role in early rehabilitation after TKR and THR. Appropriate measures have to be taken to improve the prescribing pattern so as to adhere with the WHO prescribing indicators. Multidrug therapy had leads to increased drug interactions. Adhering to the appropriate guidelines can reduce the risk of drug interactions and can also reduce the cost of treatment.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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