Efficacy and Cost Effectiveness of Universal Preoperative Iron Studies in Total Hip and Knee Arthroplasty

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Abstract

Background

Prevalence of anaemia in patients planned for total hip and knee arthroplasty is about 20%. Optimising preoperative haemoglobin levels by iron supplementation has been shown to decrease transfusion rates, complications and associated morbidity. The need for universal screening with iron studies of all elective arthroplasty patients is not clearly defined at present.

Methods

Retrospective review of 2 sequential cohorts of patients undergoing primary hip or knee arthroplasty by a single surgeon at a single centre between January 2013 and December 2017. The first group of patients underwent pre-operative iron studies only if found to be anaemic, with a haemoglobin below 12g/dL. From January 2015 all patients irrespective of the presence of anaemia were screened with a complete iron profile before surgery. Patients with a confirmed iron deficiency were administered with intravenous iron prior to surgery. The 2 cohorts were compared with regards to blood transfusion rate post-operatively and cost efficiency for universal screening with iron studies.

Results

There was a net decrease in allogenic blood transfusion rate from 4.76–2.92% when universal iron studies were introduced but the difference was not statistically significant. Obtaining universal pre-operative iron studies is cost neutral with the price of allogenic blood transfusion in a similar cohort. We also diagnosed 5 patients with occult malignancies.

Conclusions

Universal screening with pre-operative iron studies and iron infusion in elective arthroplasty patients may reduce allogenic blood requirements and is cost neutral. An additional benefit is the potential to diagnose asymptomatic malignancies. Further studies are required to show the true benefit of universal pre-operative iron screening.

Introduction

The prevalence of anaemia among patients undergoing elective total knee (TKA) and hip arthroplasty (THA) has been demonstrated to be significant, ranging between 19 to 44%, and increases with age (1–3). One of the major risk factors for requiring allogenic blood post total joint replacement is pre-operative anaemia. Allogenic blood transfusion has been associated with increased post-operative infection rates, length of hospital stay and mortality and morbidity (3). Pre-operative detection, evaluation and correction

of anaemia reduces the need for allogenic blood and the incidence of complications (4). The fundamental aim of blood management in THA and TKA is to avoid allogenic blood.

Iron deficiency is one of the leading causes of anaemia, accounting for one third of anaemia cases (5). However symptomatic iron deficiency can occur independent of anaemia. Iron deficiency on its own can cause lethargy, may impair preoperative haemoglobin (Hb) optimisation and delay post op Hb recovery and is associated with increased post-operative fatigue and hospital stay (6, 7). In a study of 715 elective orthopaedic patients, 18% of patients were found to be iron deficient in the absence of anaemia (8). Over half of the body's iron is stored in Hb, while approximately another twenty five percent is stored intracellularly as ferrous bound to ferritin protein. These two biochemical markers are important indicators for patient recovery in post-operative period as they reflect the iron levels in the body. The function of ferritin is to replenish iron stores for heme synthesis (9)

Contemporary practice in THA and TKA is to optimise red cell count in the peri-operative period using a variety of methods. These include iron supplementation; erythropoietin; and cell salvage reinfusion (10). Parenteral iron has been shown to be effective by avoiding oral compliance issues and increases Hb levels within 3 weeks. There is however a paucity of evidence available regarding the use of screening iron studies and intravenous iron infusion pre-operatively with its impact on rates of allogenic blood transfusion in elective orthopaedic surgery (11).

We have been utilising a blood conservation strategy algorithm at our institution, which includes preoperative iron studies in all patients planned for elective THA and TKA surgery from January 2015 (10). Patients with iron deficiency (Serum Iron < 5 μ mol/l or Serum Ferritin < 100, TSAT < 20%) were treated with an intravenous iron infusion pre-operatively, irrespective of pre-operative Hb level. The primary aim of this study is to assess whether our protocol of performing universal iron studies on all patients planned for elective joint replacement surgery helped in decreasing transfusion rates. The secondary aim is to assess the cost effectiveness of preoperative iron studies in elective THA and TKA.

The study hypothesis is that routine pre-operative iron studies in patients undergoing elective THA and TKA is effective in reducing allogenic transfusion rate and is cost effective.

Methods

Study design

A retrospective review of 2 sequential cohorts of patients who underwent primary THA or TKA under a single surgeon between January 2013 and December 2017 was performed. Universal screening for iron deficiency of all patients irrespective of Hb level was introduced as part of the pre-operative protocol from January 2015. Prior to this only patients found to be anaemic, defined as Hb level less than 12g/dL, were investigated with iron studies and this formed the comparator control group for the study. Between the 2 sequential groups of patients, no other change in patient management or surgical technique was introduced and the surgical time was comparable. Data was collected by review of the hospital records

and surgeon's electronic patient files. Ethics approval for the study was obtained by hospital Research and Ethics Committee.

Demographics of the two study populations are shown in Table 1. The iron studies comprised serum iron, serum ferritin, serum transferrin, serum total iron binding capacity (TIBC), and serum transferrin saturation (TSAT). Patients with studies indicating iron deficiency were referred to a haematologist, who investigated the cause and administered intravenous iron infusion as appropriate pre surgery. Iron transfusions comprised a single dose of 500-1000mg intravenous Ferritin carboxy maltose, administered in a day stay unit, given a minimum 4 weeks before surgery. The primary outcome measure of the study is blood transfusion rate between the 2 cohorts. Secondary outcome measures such as pre and post-operative Hb levels, per operative blood loss, and rates of iron transfusion were also collected. Data in the universal iron screening cohort, regarding patients who were diagnosed to have incidental malignancies on further investigation, was also collected.

Table 1
Comparison of cohorts pre and post universal screening

	2013–2015 (Pre universal screening group)	2015–2017 (Universal screening group)	P-value
Number	420	514	
Age - mean (SD)	71.1 (9.26)	71.7 (9.51)	0.3324
Gender (M:F)	200:220	239:275	0.9805
Side (Right:Left)	195:225	271:243	0.0484
THA:TKA	220:200	296:218	0.9151
BMI – mean (SD)	30.12 (5.60)	29.56 (5.67)	0.1317
Haemoglobin (pre op) – mean (SD)	134.97gm/dl (12.33)	138.33gm/dl (12.91)	0.0001
Iron deficiency anaemia	105 (25%)	180 (35%)	0.7829
Iron infusion rate	21 (5%)	71 (13.8%)	< 0.0001
Blood Transfusion rate	20 (4.8%)	15 (2.9%)	0.0886

All THA were performed through an anterolateral approach in the lateral position. Uncemented acetabular and femoral components were used, with no drain. All TKA were performed using computer navigation without tourniquet, using cemented components and routine patella resurfacing. A subcutaneous suction drains outside the joint cavity was used in TKA, with the drain removed within 24 hours after surgery. Intra-operative cell salvage was used in all cases with autologous re-infusion if sufficient blood was

salvaged. After implantation of components, topical tranexamic acid (3gm diluted in 20 ml N/saline) was instilled for 5 minutes to the surgical site prior to final lavage and closure.

Patients were ambulated on the day of surgery. Venous thromboembolism prophylaxis comprised of enoxaparin 40mg daily, commenced 4 hours post-operatively until discharge from hospital. Patients were discharged on aspirin for 6 weeks post-operatively. For patients on warfarin pre-operatively, this was continued during the peri-operative period. Warfarin dose was adjusted leading to surgery, aiming for an International Normalization Ratio (INR) of 2 on the day of surgery. The warfarin was restarted the night of surgery, with bridging enoxaparin if the INR fell below 2.

Data collected included demographics, body mass index (BMI), preoperative haemoglobin (Early Hb), iron parameters (Serum iron, Total Iron binding capacity, Serum Transferrin and Serum Ferritin), Haemoglobin post iron transfusion (Late Hb) and post operatively (Post-op Hb), perioperative blood loss, type of anesthesia, ASA grade and type of anticoagulation, total blood loss, blood collected by cell salvage and Hb change between pre-operative and day 2 post-operative. Anaemia in our study is defined as Hb less than 13g/dL in males and less than 12g/dL in females. The transfusion trigger post-operatively was Hb less than 8g/dL or symptomatic anaemia with Hb less than 10g/dL and co-existing co-morbidities

Statistical methods

Descriptive statistics for iron variables were presented for all data and by iron transfusion (performed or not performed), depending on the distribution of the data with mean and standard deviation presented for normally distributed variables. Independent t-tests were performed to compare continuous iron variables between the two cohorts.

Bivariate binary logistic regressions were performed for the outcome: blood transfusion versus demographic and blood-related predictors. A multivariable model was performed including previous iron transfusion and variables with P value < 0.2 on bivariate regression.

Bivariate linear regressions were performed for the outcomes: blood loss, RBC collected and HB drop (in separate models) versus demographic and blood-related predictors. A multivariable model was performed including previous iron transfusion and variables with P value < 0.2 on bivariate regression. Assumptions of a linear model were checked by inspection of histograms and scatter plots of residuals and predicted values.

A cross tabulation was performed for Iron deficiency anaemia versus general anemia, with associated Chi-Square P value.

Results

Nine hundred and thirty-four patients from 2013 to 2017 were included in the study. There were 420 patients in the group prior to routine iron studies (control group) and 514 in the cohort who underwent

routine iron deficiency screening (treatment group). The overall blood transfusion rate in the control group was 20/420 (4.8%) and in the treatment group was 15/514 (2.9%) with 5 following THA and 10 following TKA. Table 1 shows the demographics, iron deficiency anemia rates, iron transfusion and blood transfusion rates between the 2 cohorts. There were no major/minor side effects following the iron transfusion. There was an increase in the average Hb levels of 0.34gm/dl because of the universal screening protocol which was statistically significant ($p < 0.0001$). Though there was a reduction in blood transfusion rates this was not statistically significant (Chi-Square P value = 0.0980).

In the 514 patients in treatment group, 9.2% were detected to have anaemia of which 30% were iron deficient. Amongst the treatment cohort with normal Hb, 34.6% were found to be iron deficient (Table 2). Iron infusions were administered to 71 of 514 (13.8%) patients, with 14.4% in THA and 13.5% in TKA.

Table 2
Prevalence of anaemia and iron deficiency in joint replacement patients

	Iron deficiency		Total	P value
Anaemia	Yes	No		0.5990
Yes	12	27	39 (9.24%)	
No	134	249	383 (90.76%)	
Total	146 (35%)	276 (65%)	422	

Tables 3a and 4a outlines the distribution of iron indices, early, late and post-operative hemoglobin rates amongst the hip and knee replacement groups respectively, and in those patients, who had iron infusion as opposed to those who did not. These results show that there was a significant improvement in the Hb levels of around 0.3gm/dl following the infusion protocol. The decrease in the Hb levels postoperatively was similar in the iron transfusion group and non-iron transfusion groups. Table 3b and 4b shows comparable demographics for age, BMI and blood loss for both hip and knee cohorts.

Table 3

a. Descriptive statistics for iron variables comparing Iron transfusion group versus Non-Iron transfusion group (Total Knee Arthroplasty-TKA)

Iron variable	All data (mean(SD)) N = 296	Iron transfusion (mean(SD)) N = 38	No iron infusion (mean(SD)) N = 258	Independent T-test P value
S Iron (5–30 umol/l)	15.5 (5.1)	11.9 (4.1)	16.1 (5.0)	< 0.0001
Transferrin (1.9- 3.1gm/l)	2.5 (0.4)	2.8 (0.4)	2.5 (0.3)	0.0013
TIBC (47–77 umol/l)	62.8 (8.9)	69.0 (10.8)	61.9 (8.2)	0.0015
Tran satrn (20– 45%)	25.7 (10.7)	18.1 (6.4)	26.9 (10.7)	< 0.0001
Ferritin (30–300 ug/l)	176.1 (170.3)	51.0 (30.4)	196.0 (175.0)	< 0.0001
Early Hb (gm/dl)	138.81 (11.63)	130.29 (12.22)	140.18 (10.95)	< 0.0001
Late Hb (gm/dl)	138.35 (12.04)	132.25 (13.01)	139.22 (11.67)	0.0011
Post op Hb (gm/dl)	112.18 (13.38)	105.41 (14.44)	113.22 (12.93)	0.0009
Intraoperative Blood salvage rate	47.6%	45%	52%	0.4211*
*Chi-Square Test P value				

Table 3

b. TKA data: Descriptive statistics of
demographics

Variable	Mean	Standard deviation
Current Age	72.40	8.47
BMI	30.20	5.78
Blood Loss	331.51	144.63
RBC Collected	176.82	98.54
Hb,Drop	2.65	0.84

Table 4

a. Descriptive statistics for iron variables comparing Iron transfusion group versus Non-Iron transfusion group (Total Hip Arthroplasty-THA)

Iron variable	All data (mean(SD)) N = 216	Iron transfusion (mean(SD)) N = 33	No iron infusion (mean(SD)) N = 183	Independent T-test P value
S Iron (5–30 umol/l)	15.4 (5.2)	13.1 (4.7)	15.9 (5.1)	0.0067
Transferrin (1.9- 3.1gm/l)	2.5 (0.4)	2.7 (0.3)	2.4 (0.30)	< 0.0001
TIBC (47–77 umol/l)	62.0 (8.9)	68.3 (8.0)	60.7 (8.5)	< 0.0001
Tran satrn (20– 45%)	25.6 (9.3)	19.8 (8.6)	26.8 (9.0)	0.0001
Ferritin (30–300 ug/l)	181.5 (149.2)	59.8 (54.4)	208.5 (150.2)	< 0.0001
Early Hb (gm/dl)	138.95 (13.64)	130.39 (14.05)	140.64 (12.95)	0.0002
Late Hb (gm/dl)	138.30 (14.05)	134.12 (13.23)	139.08 (14.10)	0.0626
Post op Hb (gm/dl)	117.26 (13.44)	111.55 (11.33)	118.26 (13.56)	0.0100
Intraoperative Blood salvage rate	53.2%	60%	50%	0.2912*
*Chi-Square Test P value				

Table 4

b. THA data: Descriptive statistics of demographics

Variable	Mean	Standard deviation
Current_Age	68.48	9.91
BMI	28.67	5.40
Blood Loss	324.78	133.32
RBC Collected	168.72	81.91
Hb Drop	2.07	0.85

Iron infusions were found to be predictive for blood transfusions among TKR patients but not among THR patients (Tables 5, and 6). Low pre-operative Hb was also strongly predictive of blood transfusion rates. Other factors that were positively associated with increased perioperative blood loss and lower post op Hb included general anaesthesia, use of warfarin and rivaroxaban as anticoagulants, and female gender. (Table 5,6)

Table 5
Factors affecting Blood transfusion/Blood loss in TKA

Total Knee Arthroplasty data OR/Estimate (95% CI) p value Global p value
Bivariate analysis*
Previous Iron transfusion 13(3, 56) 0.0007
Multivariable analysis for outcome: Blood Transfusion*
Late pre-operative Haemoglobin 0.80 (0.70, 0.91) * 0.0010
Multivariable analysis for outcome: Blood Loss
Type of Anaesthesia 0.0111
Spinal/GA vs GA -111.4 (-185.6,-37.4) 0.0032
Spinal vs GA -71.3 (-135.2,-7.5) 0.0286
Anticoagulants <.0001
0 vs 2** -274 (-417, -130) 0.0002
0 vs 3* * -232.7 (-403.0, -62.5) 0.0074
Multivariable analysis for outcome: Haemoglobin drop
BMI -0.02(-0.04,0.0) 0.0120
Gender (Male vs Female) -0.35(-0.56,-0.15) 0.0007
Anticoagulants 0.0288
0 vs 2** -0.67 (-1.26, -0.08) 0.0249
1 vs 2** -1.44 (-2.41, -0.48) 0.0034
Late pre-operative Haemoglobin 0.02 (0.01, 0.03) <.0001
<i>*Binary logistic regression – Odds Ratio (95% confidence interval); modelling the probability that Blood Transfusion='Yes'</i>
<i>**Anti coag (0 = Clexane, 1 = Aspirin, 2 = Warfarin, 3 = All Others [Rivaroxaban, Apixaban])</i>

Table 6
Factors affecting Blood transfusion/Blood loss in THA

Total Hip Arthroplasty data OR/Estimate (95%CI) p value Global p value
Multi variable analysis for outcome: Blood Transfusion*
Late pre-operative Haemoglobin 0.89 (0.83,0.95) 0.0006
Multivariable analysis for outcome: RBC collected
Iron transfusion Yes vs No 60.2 (22.3, 98.1) 0.0019
Type of Anaesthesia
Spinal vs GA -38.7 (-68.9, -8.4) 0.0375
Late pre-operative Haemoglobin 1.46 (0.43, 2.50) 0.0056
Multivariable analysis for outcome: Blood Loss
Iron transfusion Yes vs No 85.3 (11.7, 158.8) 0.0231
Anticoagulants 0.0496
0 vs 3 ** 162.6 (-294.1, -31.1) 0.0153
2 vs 3 ** -182.4 (-363.1, -1.7) 0.0478
Multivariable analysis for outcome: Hb Drop
Late pre-operative Haemoglobin 0.02(0.01,0.03) <0.0001
<i>*Binary logistic model – Odds ratio (95% CI) – modelling the probability that blood transfusion = Yes</i>
<i>**Anti coag (0 = Clexane, 1 = Aspirin, 2 = Warfarin, 3 = All Others [Rivaroxaban, Apixaban])</i>

Amongst our elective THA and TKA cohort, we diagnosed 10 patients, following further evaluation of their iron deficiency with underlying gastric causes or malignant disease which were subsequently treated prior to joint arthroplasty surgery. These are listed in Table 7.

Table 7 Pathology Diagnosed following evaluation of Iron deficiency anaemia

Gastric erosions/Gastric ulcer	5
Bowel Cancer	3
Haematological cancer	2 (1-Myelodysplastic syndrome, 1- Chronic myeloid leukaemia)

For cost effectiveness of routine pre-operative iron studies, we calculated the numbers needed to treat (NNT) of our cohort as 49.06. This is derived from the formula, $NNT = 1 / \text{incidence in control group} - \text{incidence in treated group}$.

For iron infusion- $NNT = 71/514 \times 49.06 = 6.8$

Cost for iron infusion: $6.8 \times \$135$ (per iron infusion) = \$ 918 (\$=Australian dollar/AUD)

For iron studies - $NNT = 433/514 \times 49.06 = 41.33$

Cost for iron studies: $41.33 \times \$30$ (per iron study) = \$ 1,240.

Total costs for iron protocol = Iron infusion costs + Iron studies costs (\$918+ \$1,240) = \$2,158

For Blood transfusion

$(2 \times 15/512) \times 49.06 = 2.86$ units (each patient had 2 units of blood)

Costs for Blood transfusion: $2.86 \times \$700$ (per blood unit) = \$2,004.

Hence our universal iron screening and iron infusion protocol is cost neutral with the expense of allogenic blood transfusion (\$2,158 vs \$2,004) in this patient cohort.

Discussion

Universal screening with preoperative iron studies and iron infusion in elective THA and TKA patients in our study decreased allogenic transfusion rates post operatively but was not statistically significant. We believe part of the reason why the allogenic transfusion rate was not significant between the 2 groups is our transfusion rate was already very low in the control patients, because of our blood management protocols (12). Universal screening with iron studies was essentially equivalent cost compared to the savings from reduction in blood transfusion rates. However, we believe pre-operative iron screening is still advantageous, as our cost calculation did not factor into account possible complications and increased length of hospital stay which often result from allogenic blood transfusion.

Pre-operative anaemia occurred in 1 out of 10 patients presenting for THA and TKA, of which Iron deficiency anaemia was the cause in one third, which is similar to the results of other studies (13). Intravenous iron infusion rapidly increases the pre-operative Hb levels, bypasses the effects of oral compliance, and the effect of hepcidin in patients with anaemia of chronic disease. It can help to decrease allogenic transfusion rates, reduce post op Hb drop after surgical blood loss and hasten the post-operative recovery rate of Hb. The average decrease in Hb following THA and TKA is approximately 4gm (14). In our treatment group, we were able to increase the Hb preoperatively by average 0.2 gm in TKA and 0.3gm in THA cohort. Moreover, the universal screening protocol (2015–2017) significantly increased the average Hb by a mean of 0.3gm/dl ($p < 0.0001$), as compared to the cohort prior to 2015.

One third of our patients who had normal Hb had iron deficiency, and this is similar to recent studies (15). There are 2 important ramifications of this finding. Firstly, iron deficiency on its own, even in the absence of anaemia, can cause lethargy and tiredness. This may then hinder a patient's ability to rehabilitate following surgery (16). Secondly, iron deficiency is a sign of potential malignancy, especially after the age

of 60. Eight-15% of patients with iron deficiency anaemia will have a gastro intestinal (GI) malignancy (17) and colorectal carcinoma presents with iron deficiency anaemia in 50% of cases(18). More importantly patients with iron deficiency alone in the absence of anaemia have been found to have increased risk of GI malignancy after 2 years (19). Following commencement of routine iron screening in our elective THA and TKA patients, we diagnosed 5 malignancies in patients who were otherwise asymptomatic and unaware of their diagnosis. The incidental benefit of diagnosing malignancies early in these patients cannot be discounted, which would not have been possible without universal iron studies which helped us identify these patients and instigate early treatment.

As has been demonstrated in previous studies, gender(female), type of anesthesia (GA), type of surgery (THR) and low pre-operative Hb were associated with increased allogenic blood transfusion risk(20, 21). Interestingly, we were able to show that pre-operative iron deficiency correlated with blood loss and iron transfusions were a strong prognostic factor for having post op blood transfusions. This was seen only on bivariate analysis and in the TKA group. The higher blood transfusion rates among patients who underwent iron transfusion could probably be explained by the lower baseline Hb levels and impaired erythropoiesis. Of the 14 patients transfused, 3 had blood disorders and 4 had multiple comorbidities with anaemia of chronic disease and consequent impaired erythropoiesis, while 4 had ischemic heart disease with stents with a low transfusion trigger.

The weaknesses of this study include the retrospective design and method of data collection via medical record review. There may have been recall bias and inaccurate data entry into the medical record which could have affected the results. Our findings may not be applicable to all regions of the world or all patient ethnicities. Additionally, as the study is a single surgeon series, surgical techniques and protocols may also vary and influence the outcomes and conclusions. Finally, as our allogenic transfusion rate in the control group was already low, the study may be underpowered and hence we were unable to demonstrate statistical significance with allogenic blood transfusion rates. Nevertheless, we believe our findings still highlight several important issues and is relevant to surgeons undertaking THA and TKA, especially so at present, where the focus has shifted to short stay or day care surgery. Correcting preoperative iron deficiency anaemia, through universal iron studies may facilitate this. The study is a single surgeon series with a uniform protocol and no change in surgical pathway apart from iron studies between the 2 comparison groups.

Transfusion rates for joint replacements have been reported to be about 18% for knee and 22% for hip arthroplasties(22), but can range from 13–87%, showing (23) the high variability in clinical practice. Our low allogenic transfusion rates were decreased even further by routine pre-operative iron studies and iron infusion protocol. This could also partly explain why we were not able to show a statistically significant decrease in blood transfusion rates or cost effectiveness. While Medicare cost of blood transfusion is \$700 per unit, the cost of maintaining blood bank and personnel make the actual costs of a unit of blood about 2–5 times more(24). The true cost of allogenic blood should also factor complications and increased length of hospital stay often associated. Adding hidden costs and having a larger study group might have shown cost effectiveness with our protocol. A recent systematic review investigating pre-

operative Iron transfusions showed a definite decrease in blood transfusions, length of hospital stay and post-operative infections(25).

Conclusion

Universal screening with pre-operative iron studies and iron infusion in elective total hip and knee arthroplasty patients may reduce allogenic blood requirements and is cost neutral. Additional benefit is the potential to diagnose asymptomatic malignancies. Further prospective studies with greater power may be required to show the true benefit of universal pre-operative iron screening by factoring into account length of hospital stay, cost of complications and maintenance of the blood bank, and cost benefits of early diagnosis of occult malignancies.

List Of Abbreviations

TKA- Total knee arthroplasty, THA- Total Hip arthroplasty

Hb- Haemoglobin, TIBC- Total iron binding capacity,

TSAT- Transferrin saturation, BMI- Body mass index

ASA- American society of anesthesiologists, GA- General anesthesia

NNT- Numbers needed to treat, GI- Gastrointestinal

Declarations

Ethics approval and consent to participate

Ethics committee approval for this study was obtained from the Greenslopes Research and Ethics committee for this study(protocol18/44) conducted at the John Flynn hospital, Queensland, Australia, on 30/10/2018.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Competing interests

The authors declare they have no competing interests.

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This study did not receive any funding.

Authors' contributions

Authors VDV and DN helped in collecting, tabulating and analysing the data from the hospital records. Author DL was the primary surgeon, who conceptualised the study and developed the protocols and was a major contributor for the study. Author SE was primarily helpful in the statistical analysis. Authors VDV and DL helped in writing and reviewing the manuscript. All authors have contributed to the write up and read and approved the final manuscript.

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