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FDLKAT001

Dissertation for Master of Medicine (MMED) in Anaesthesia
University of Cape Town

Anaemia in a South African colorectal ERAS programme – identifying the prevalence and predictors of preoperative anaemia and the effect on post-operative complications and length of stay

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List of documents included:

1. Acknowledgements
2. Declaration
3. Plagiarism declaration
4. Thesis
5. Ethics approval letter

ACKNOWLEDGEMENTS

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FORMAT

This is a journal ready manuscript. Study is not yet published. Target journal is the South African Medical Journal (SAMJ). Manuscript has not yet been submitted for review. UK English spelling has been used throughout the manuscript.

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Title

Anaemia in a South African colorectal ERAS programme – identifying the prevalence and predictors of preoperative anaemia and the effect on post-operative complications and length of stay

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Abstract

Background: Anaemia is a widespread public health problem associated with increased mortality and morbidity. In a surgical population, the prevalence of preoperative anaemia often exceeds that of the general population. Elective colorectal patients often have multiple risk factors for preoperative anaemia. The fourth updated ERAS Society guidelines for optimal perioperative care in colorectal surgery include specific recommendations for screening and treatment of preoperative anaemia as well as utilising restrictive blood transfusion practice. Assessing the prevalence and predictors of anaemia and outcomes in

this population may allow for improved preoperative assessment and treatment of colorectal patients in a resource limited setting.

Objectives: The primary objective of this retrospective study was to determine the prevalence of anaemia in the colorectal surgical population who were part of the enhanced recovery after surgery (ERAS) programme at a tertiary level hospital in the Western Cape, South Africa. Secondary objectives were to determine independent risk factors of preoperative anaemia, and the effect of anaemia on post-operative complications and length of stay after elective colorectal surgery.

Methods: We performed a secondary analysis of data collected for the colorectal surgical ERAS programme. Data of 260 patients was reviewed from the initiation of the database 01 September 2016 to 30 September 2019. Three regression analyses were performed as part of the secondary objective to determine the risk factors for preoperative anaemia and predictors for postoperative complications and length of hospital stay. Patients were defined as anaemic if their haemoglobin was less than 13.0 g/dL.

Results: The prevalence of preoperative anaemia was 157/260 (60.3%). Female sex (odds ratio (OR) 2.44, 95% confidence interval (CI) 1.43 – 4.18; p=0.001) and the presence of malignancy (OR 2.42, CI 1.26- 4.67; p=0.008) showed a significant association with anaemia. Anaemia was not associated with increased risk of post-operative complications or length of hospital stay.

Conclusion: South African colorectal surgical patients in an enhanced recovery after surgery programme have a higher prevalence of preoperative anaemia compared to the general surgical population. Predictors of preoperative anaemia in this population included female sex and the presence of malignancy. Long waiting lists for patients awaiting elective colorectal surgery allow time for evaluation and optimisation of patients at risk for anaemia preoperatively.

Keywords: Anaemia, colorectal surgery, ERAS

Introduction

Anaemia is a widespread public health problem affecting one out of every three people globally. [1] However in a surgical population, the prevalence of preoperative anaemia can exceed that of the general population. Depending on associated comorbidity, gender, age and underlying pathology, prevalence can be as high as 75%. [2]

The South African Surgical Outcomes Study (SASOS) cohort showed that compared to higher income countries, the South African surgical population had a higher prevalence of anaemia and that this was associated with increased in-hospital mortality (odds ratio (OR) 1.657, 95% confidence interval (CI) 1.055 - 2.602; p=0.028). In the SASOS cohort the prevalence of preoperative anaemia was 47.8%. [3][4]

Elective colorectal surgery is frequently classified as high risk in terms of complications and commonly indicated for patients with colorectal cancer, diverticular or inflammatory disease. These patients often have multiple factors causing preoperative anaemia. Due to blood loss or chronic inflammation, the majority of patients presenting for colorectal surgery will have iron deficiency anaemia. [5–7]

Preoperative anaemia is linked with an increased risk of major adverse outcomes including mortality, allogeneic blood transfusion, acute kidney injury, intensive care admissions, length of hospital stay and infection. [8] [9] In patients undergoing surgery for colorectal cancer, preoperative anaemia has been associated with decreased disease-free and overall survival. [10] However, the administration of blood products to correct anaemia perioperatively is also known to be associated with increased morbidity and mortality in general, as well as in colorectal cancer specifically. [6,10]

The Enhanced Recovery After Surgery (ERAS) care pathway for colorectal surgery is a patient centred, multi-disciplinary team approach to perioperative care. It is aimed at reducing the perioperative physiological stress response and immune suppression, while accelerating recovery after surgery. The fourth updated ERAS Society guidelines for optimal perioperative care in colorectal surgery were released in 2018 which include specific

recommendations for screening and treatment of preoperative anaemia as well as utilising restrictive blood transfusion practice.[6,11] The quality of evidence for the recommendation was high and management of anaemia is strongly recommended.

Determining the prevalence and predictors of anaemia and outcomes in this population group may improve the preoperative assessment and treatment of elective colorectal patients. The primary objective of this retrospective study was to determine the prevalence of anaemia in the colorectal surgical population who were part of the enhanced recovery after surgery (ERAS) programme at a tertiary level hospital in the Western Cape, South Africa. Secondary objectives were to determine the effect of independent risk factors on preoperative anaemia, post-operative complications and length of stay after elective colorectal surgery.

Methods

This is a retrospective study of colorectal patients presenting for elective surgery from the colorectal Enhanced Recovery After Surgery (ERAS) database at Groote Schuur Hospital, a tertiary level hospital in the Western Cape, South Africa (University of Cape Town Human Research Ethics Committee ref no. HREC R009/2015). Data was reviewed from the initiation of the database 01 September 2016 to 30 September 2019.

The ERAS program applies to all patients referred for elective colorectal surgery at Groote Schuur Hospital. All patients for this study were selected from this existing database. The data entered into the database during the timeframe specified above, was screened and patients were excluded from our review if they were under 18 years of age, did not undergo their planned elective surgery or did not have a preoperative haemoglobin recorded on the database system. A further 2 patients were removed from analysis to prevent a skewed model performance and large standard error. (Figure 1). No further codes, algorithms or linkage of databases were used in this study.

Baseline demographic and clinical data were recorded on an Excel spreadsheet. Data information collected included: age, sex, American Society of Anesthesiology (ASA) Physical Status Classification, presence of malignancy, preoperative chemotherapy, preoperative haemoglobin, operative severity, Clavien-Dindo complication score (see appendix) and length of hospital stay. Haemoglobin and operative severity data was collected from the P-POSSUM score that is calculated prior to surgery. Operative severity was graded into minor, moderate and major. Patients with missing data were excluded from the analysis. Any source of bias in reporting in the database could not be further verified. Investigators had full access to the database and no cleaning methods were applied. Only in-hospital data were used in this study. Patient follow-up data were included in the database.

According to the World Health Organisation (WHO) classification, male patients over 15 years living at sea level are anaemic if the haemoglobin is less than 13 g/dL and non-pregnant females if less than 12 g/dL.[12] We used a cut-off of 13 g/dL, regardless of sex, as in surgical patients the intraoperative blood loss is comparable irrespective if male or

female.[13] Thus females may experience increased blood losses compared to males, as they have a lower circulating blood volume. In female cardiac surgery patients, an Hb between 12 and 12.9 g/dL has been associated with increased hospital stay and transfusion rates.[9] We further classified anaemia according to severity based on the WHO classification. The ranges of which are applicable only to patients living at sea level. Severity of anaemia was defined as mild (11 – 12.9 g/dL), moderate (8 – 10.9 g/dL) or severe (< 8 g/dL). [12]

Categorical variables were described as proportions and compared using chi-square tests. Continuous variables were described as mean and standard deviation if normally distributed or median and inter-quartile range (IQR) if not normally distributed. Three regression analyses were performed as part of the secondary objective to determine the risk factors for preoperative anaemia and predictors for postoperative complications and length of hospital stay in colorectal patients. A binary logistic regression analysis was used to determine risk factors for preoperative anaemia. The risk factors (independent variables - sex, malignancy, preoperative chemotherapy and ASA grading) were entered into the model based on clinical plausibility and based on our clinical understanding of their associated outcomes. A binary logistic regression analysis was also used to see the effect of independent variables (sex, age, malignancy, anaemia, preoperative chemotherapy, ASA grade and operative severity) on postoperative complications. A linear regression analysis was performed to identify the effect of independent predictors (sex, age, malignancy, anaemia, preoperative chemotherapy, ASA grading and operative severity) on length of stay after initial colorectal elective surgery. The Statistical Package for the Social Sciences (SPSS) version 24 (SPSS, Chicago, IL, USA) was used for the analyses.

Results

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) diagram in figure 1 shows how the final dataset was derived. After the initial screening of 282 patients which were entered into the database, 260 patients were eligible for inclusion in the data analysis. The prevalence of preoperative anaemia in this patient group was 157/260 (60.3%), with 92/ 260 (35.5%) patients presenting with mild anaemia, 54/260 (20.7%) with moderate anaemia and 11/260 (4.2%) with severe anaemia. The mean (SD) haemoglobin value was 12.1 (±2.1) g/dL.

Females comprised 51.9% of the cohort. The mean age in the overall cohort was 57.2 ±13.5 years. Of the patients included, 57.7% (150/260) had a cancer diagnosis, of whom 49.3% (74/150) received chemotherapy preoperatively.

In the logistic regression analysis to determine the predictors of preoperative anaemia, female sex (odds ratio (OR) 2.44, 95% confidence interval (CI) 1.43 – 4.18; p=0.001) and the presence of malignancy (OR 2.42, CI 1.26- 4.67; p=0.008) showed a significant association with anaemia. In the analysis to establish factors increasing risk of developing post-operative complications, major surgery had the strongest significant association (OR 2.84, CI 1.27-6.38; p=0.011). Major surgery was also the most significant contributing factor to increased length of post-operative hospital stay (OR 3.79, CI 1.57-6.01; p=0.001) in the linear regression analysis. Anaemia was not associated with increased risk of post-operative complications (OR 1.02, CI 0.89-1.18; p=0.78) or length of hospital stay (OR 0.78, CI -0.37-0.51; p=0.74).

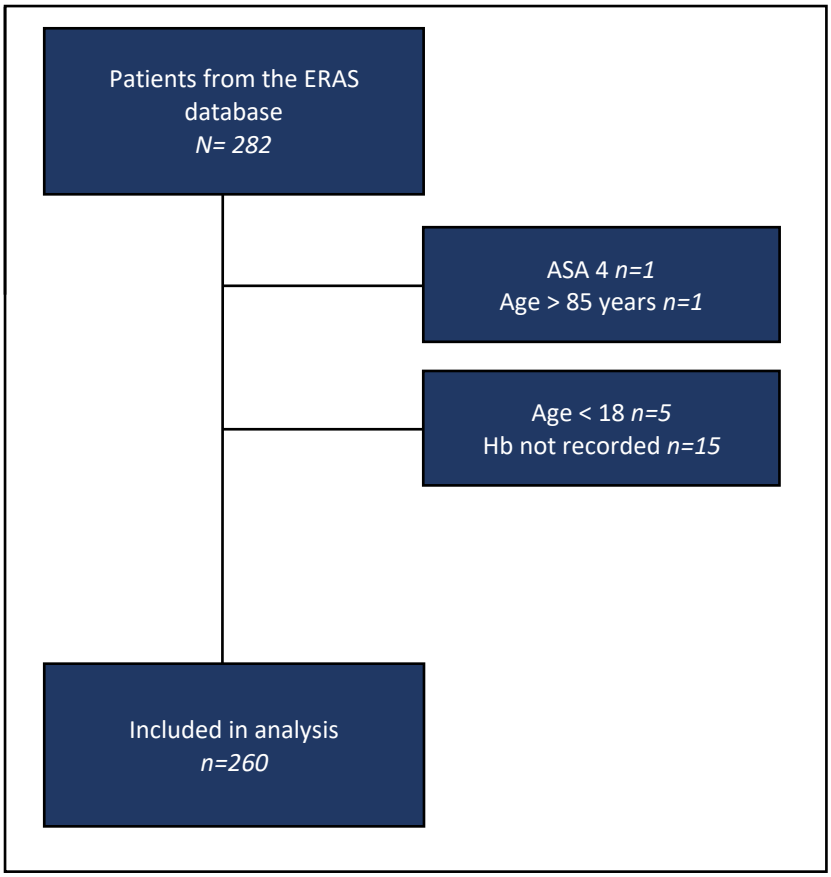

Figure 1. Flow diagram of patient recruitment for study (ERAS = enhanced recovery after surgery, Hb = haemoglobin, ASA = American Society of Anesthesiology Physical Status Classification System)

Table 1. Demographics of patients with and without anaemia

Table 1. Demographics of patients with and without anaemia

	Total (*N*=260)	Anaemic (*n*=157)	Not anaemic (*n*=103)	*p*-value
Age (years), mean (SD)	57.2 (13.5)	57.1 (13.3)	57.5 (13.7)	0.7
Hb (g/dL) mean (SD)	12.1 (2.1)	10.8 (1.6)	14.0 (0.9)	<0.0001
Female, *n* (%)	135 (51.9)	93 (68.8)	42 (31.1)	0.001
ASA, *n* (%)				0.10
1	31	16 (51.6)	15 (48.4)	
2	143	76 (53.1)	67 (46.9)	
3	86	62 (72.1)	24 (27.9)	
4	0	0	0	

Grade of surgery, *n* (%)				0.005
Minor	2	0	2	
Moderate	76	35 (46)	41 (53.9)	
Major	182	118 (64.8)	64 (35.1)	
Malignancy	150 (57.7)	106 (70.6)	44 (29.3)	<0.0001
Preoperative chemotherapy	74 (28.5)	54 (72.9)	20 (27)	0.003
n (%)				
Hb = haemoglobin, ASA = American Society of Anesthesiologists				

Table 2. Patients with anaemia according to proposed modification of the WHO classification [13]

Anaemia subtype	Total N=260 (%)
No anaemia (Hb>13 g/dL)	103 (39.6)
Mild (Hb 11-12.9 g/dL)	92 (35.4)
Moderate (Hb 8-10.9 g/dL)	54 (20.8)
Severe (Hb <8 g/dL)	11 (4.2)
Hb = Haemoglobin	

Table 3. Independent predictors of preoperative anaemia

Predictors of anaemia	p-value	OR	95% CI
Female sex	0.001	2.442	1.426- 4.183
ASA grade 1	0.199	Reference	
ASA grade 2	0.573	1.273	0.550- 2.950
ASA grade 3	0.121	2.074	0.825- 5.210
Presence of malignancy	0.008	2.424	1.260- 4.665
Preoperative chemotherapy	0.296	2.424	1.260- 4.665

OR = odds ratio, CI= confidence interval, ASA= American Society of Anesthesiology

Discussion

Our study showed a high prevalence of preoperative anaemia (60.3%) in surgical patients presenting for elective colorectal surgery in an ERAS population at Groote Schuur Hospital in Cape Town, South Africa. In this population group preoperative anaemia was not associated with an increased risk for postoperative complications or increased length of stay.

This prevalence of anaemia is higher than that detected in the general surgery elective SASOS population (38.2%). However, this was based on a definition of anaemia according to the WHO. The mean haemoglobin in the SASOS population was 12.3 g/dL. Compared to other studies done in colorectal surgical populations our findings lie towards the higher end of the typical range of 30-75%.[5] More than half the patients in our study had colorectal cancer (58%) which likely contributes to the increased prevalence of anaemia. Anaemia in malignancy can be attributed to chronic gastro-intestinal blood loss, iron deficiency, bone marrow involvement or side effects of neoadjuvant chemotherapy.[5,14]

The majority of anaemia cases were classified as mild. However, the number of moderate and severe anaemic cases in this group must still be considered significant in terms of potential for preoperative anaemia optimisation. Several larger studies report that mortality in surgical patients is inversely related to the haemoglobin level and even mild anaemia is associated with increased perioperative adverse outcomes.[4,15,16]

Female sex was a significant independent predictor of preoperative anaemia in our study. This was not the case in the SASOS cohort or the multicentre study in the Western Cape that followed.[4,17] This is expected as we used a higher value to classify female surgical patients as anaemic compared to the WHO definitions. When using a cut-off of less than 12.0 g/dL, 47% of the total females in this study were anaemic. Over half of the female patients in our study with anaemia had a haemoglobin less than 10.9 g/dL (i.e. moderate anaemia). Previous studies in a South African population have shown that iron deficiency is a common cause of preoperative anaemia with a much higher proportion occurring in women (11% in males versus 50% in females).[17,18] Iron deficiency is associated with chronic conditions such as cancer and inflammatory bowel disease. This is due to decreased iron availability and

reduced iron intake secondary to inflammation, poor appetite, decreased absorption and frequent iron loss due to bleeding. These are common conditions in colorectal patients presenting for elective surgery.[19] Investigating and correcting iron deficiency anaemia may reduce the proportion of female patients with moderate anaemia presenting for colorectal surgery and thus the risk of perioperative allogeneic blood transfusions.

The 2018 colorectal ERAS society guidelines strongly recommend attempting to investigate and correct anaemia prior to surgery. It has been proposed to aim for a Hb > 13 g/dL regardless of sex preoperatively.[6,20] Our study did not investigate the cause of anaemia as it was not a part of the protocol at the time to investigate for iron deficiency. Since data collection, the colorectal surgery division has included a detailed work up and management of anaemia in their departmental ERAS guidelines. This includes use of intravenous iron transfusions where oral preparations prove inadequate or where insufficient time remains prior to surgery.

The benefits of using intravenous iron to treat preoperative anaemia remains under discussion. In the recent large multicentre PREVENTT trial intravenous iron did not reduce blood transfusion or mortality in the perioperative period.[21] It is important to note that in this study, intravenous iron was given to all anaemic patients, not exclusively to iron deficient patients, which may have diluted any positive effects and only included patients presenting for major abdominal surgery.[22] In terms of other outcomes however, treating anaemia in colorectal cancer patients with IV iron has been shown to increase preoperative Hb in the short term [23] and provide a longer-lasting haemoglobin response [24] as well as improve quality of life for patients with colorectal cancer compared to oral iron or no treatment.[25]

In our analysis anaemic patients did not have an increased risk of developing post-operative complications compared to non-anaemic patients. This is contrary to the results of other larger multicentre studies in colorectal surgical patients (a database of 23 000 patients who met inclusion criteria), where patients with severe, moderate or mild preoperative anaemia all had an increased risk for postoperative complications and a longer hospital stay.[14] Patients with severe and moderate anaemia were hospitalised approximately 2.2 and 1.4 days respectively longer than those with a normal haematocrit.[14,26] The higher proportion

of mild anaemia cases as well as the small population sample may have contributed to a lesser effect on complication rates and length of stay than what was initially expected. Our study also included minor surgeries that may have diluted the effect on outcomes in terms of complications and length of hospital stay.

Our study being a retrospective design with a small registry size (at time of data collection in 2019) unfortunately also involved incomplete data, which limited the data interpretation further. A larger sample size focusing on patients presenting for major surgery, including data on transfusion rates may correlate more with findings from the larger referenced multicentre studies.

Despite the limitations mentioned, this was the first study in South Africa specifically examining the prevalence of anaemia in an established enhanced recovery program in colorectal surgery, which highlights the high prevalence rate of anaemia in this population.

Conclusion

Colorectal surgical patients have a higher prevalence of preoperative anaemia compared to the general surgical population and anaemia is common in enhanced recovery colorectal patients in South Africa. In this retrospective observational study, anaemia had no impact on postoperative complications or length of hospital stay after elective colorectal surgery. However, as per the limitations of this study mentioned in the discussion this does not compare to larger multicentre studies and ideally all anaemic patients require optimisation prior to surgery. In this population in a resource limited country, the authors suggest directing work up for those patients who are at increased risk for preoperative anaemia such as female patients and patients with malignancy who are presenting for major surgery. The extended waiting lists for patients awaiting elective colorectal surgery allow time for assessment and optimisation of anaemia preoperatively.

Declaration: M Gibbs has received speakers fees from Vifor.

Author contribution: All equal. KN performed this work to fulfil the requirements for the MMed (Anaesthesia).

Conflicts of interest: None

Funding sources: None

References

1. Muñoz M, Gómez-Ramírez S, Kozek-Langeneker S, Shander A, Richards T, Pavía J, et al. “Fit to fly”: Overcoming barriers to preoperative haemoglobin optimization in surgical patients. Br. J. Anaesth.2015;115(1):15–24. https://doi.org/10/1093/bja/aev165
2. Goodnough LT, Shander A, Spivak JL, Waters JH, Friedman AJ, Carson JL, et al. Detection, evaluation, and management of anemia in the elective surgical patient. Anesth Analg 2005;101(6):1858–1861. https://doi.org/10.1097/01.sa.0000234704.07366.b2
3. Biccard BM, Madiba TE. The South African surgical outcomes study: A 7-day prospective observational cohort study. South African Med J 2015;105(6):465–475. https://doi.org/10.7196/samj.9435
4. Marsicano D, Hauser N, Roodt F, Cloete E, Conradie W, Morford V, et al. Preoperative anaemia and clinical outcomes in the south african surgical outcomes study. South African Med J 2018;108(10):839–846. https://doi.org/10.7196/samj.2018.v108i10.13148
5. Muñoz M, Gómez-Ramírez S, Martín-Montañez E, Auerbach M. Perioperative anemia management in colorectal cancer patients: A pragmatic approach. World J Gastroenterol 2014;20(8):1972–1985. https://doi.org/10.3748/wjg.v20.i8.1972
6. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS®) Society Recommendations: 2018. World J Surg 2019;43(3):659–695. https://doi.org/10.1007/s00268-018-4844-y
7. Patel S, Lutz JM, Panchagnula U, Bansal S. Anesthesia and perioperative management of colorectal surgical patients - specific issues (part 2). J Anaesthesiol Clin Pharmacol 2012;28(3):304–313. Available from: https://www.ncbi.nlm.nih.gov/pubmed/22869934
8. Fowler AJ, Ahmad T, Phull MK, Allard S, Gillies MA, Pearse RM. Meta-analysis of the association between preoperative anaemia and mortality after surgery. Br J Surg 2015;102(11):1314–1324. Available from: http://doi.wiley.com/10.1002/bjs.9861
9. Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery – why, who, when and how? Anaesthesia2019;74:49–57. https://doi.org/10.1111/anae.14466
10. Wilson MJ, van Haaren M, Harlaar JJ, Park HC, Bonjer HJ, Jeekel J, et al. Long-term prognostic value of preoperative anemia in patients with colorectal cancer: A systematic review and meta-analysis. Surg. Oncol.2017;26(1):96–104. Available from: http://dx.doi.org/10.1016/j.suronc.2017.01.005
11. Oodit R, Biccard B, Nelson G, Ljungqvist O, Brindle ME. ERAS Society Recommendations for Improving Perioperative Care in Low- and Middle-Income Countries Through Implementation of Existing Tools and Programs: An Urgent Need for the Surgical Safety Checklist and Enhanced Recovery After Surgery. World J. Surg.2021;45(11):3246–3248. https://doi.org/10.1007/s00268-021-06279-x
12. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (http://www.who.int/vmnis/indicators/haemoglobin.pdf), acc.

2018. https://apps.who.int/iris/handle/10665/85839
13. Butcher A, Richards T, Stanworth SJ, Klein AA. Diagnostic criteria for pre-operative anaemia–time to end sex discrimination. Anaesthesia 2017;72(7):811–814. Available from: http://doi.wiley.com/10.1111/anae.13877
14. Leichtle SW, Mouawad NJ, Lampman R, Singal B, Cleary RK. Does Preoperative Anemia Adversely Affect Colon and Rectal Surgery Outcomes? J Am Coll Surg 2011;212(2):187–194. Available from: https://doi.org/10.1016/j.jamcollsurg.2010.09.013
15. Shander A, Knight K, Thurer R, Adamson J, Spence R. Prevalence and outcomes of anemia in surgery: A systematic review of the literature. Am J Med 2004;116(7 SUPPL. 1):58–69. Available from: https://doi.org/10.1016/j.amjmed.2003.12.013
16. Musallam KM, Tamim HM, Richards T, Spahn DR, Rosendaal FR, Habbal BSN A, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. Lancet 2011;378:1396–41407. Available from: http://www.acsnsqip.org
17. Conradie WS, Biesman-Simons T, Roodt F, Nejthardt M, Davids J, Pretorius T, et al. A multicentre prospective observational study of the prevalence of preoperative anaemia and iron deficiency in adult elective surgical patients in hospitals in Western Cape Province, South Africa. South African Med J 2019;110(1):65. Available from: http://www.samj.org.za/index.php/samj/article/view/12813
18. Phatlhane D V, Zemlin AE, Matsha TE, Hoffmann M, Naidoo N, Ichihara K, et al. The iron status of a healthy South African adult population. 2016; Available from: http://dx.doi.org/10.1016/j.cca.2016.06.019
19. Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017; Feb;72(2): 233-247. https://doi.org/10.1111/anae.13773
20. Pasricha SR, Colman K, Centeno-Tablante E, Garcia-Casal MN, Peña-Rosas JP. Revisiting WHO haemoglobin thresholds to define anaemia in clinical medicine and public health. Lancet Haematol 2018;5(2):e60–62. Available from: http://www.who.int/nutrition/publications/globaltargets2025_
21. Richards T, Baikady RR, Clevenger B, Butcher A, Abeysiri S, Chau M, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet (London, England) 2020;396(10259):1353–1361. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32896294
22. Hofmann A, Gross I, Girelli D, Aapro M, Spahn DR. Iron deficiency in PREVENTT. Lancet 2021;397(10275):668–669. Available from: http://dx.doi.org/10.1016/S0140-6736(21)00226-9
23. Wilson MJ, Dekker JW, Bruns E, Borstlap W, Jeekel J, Zwaginga JJ, et al. Short-term effect of preoperative intravenous iron therapy in colorectal cancer patients with anemia: results of a cohort study. Transfusion 2018;58(3):795–803. Available from: https://onlinelibrary.wiley.com/doi/full/10.1111/trf.14456
24. Dickson EA, Keeler BD, Ng O, Kumar A, Brookes MJ, Acheson AG. Preoperative intravenous iron therapy and survival after colorectal cancer surgery: long-term results from the IVICA randomised controlled trial. Color Dis 2020;22(12):2018–2027. Available from: https://onlinelibrary.wiley.com/doi/10.1111/codi.15342

25. Keeler BD, Dickson EA, Simpson JA, Ng O, Padmanabhan H, Brookes MJ, et al. The impact of pre-operative intravenous iron on quality of life after colorectal cancer surgery: outcomes from the intravenous iron in colorectal cancer-associated anaemia (IVICA) trial. Anaesthesia 2019;74(6):714–725. Available from: https://onlinelibrary.wiley.com/doi/10.1111/anae.14659
26. Dunne JR, Malone D, Tracy JK, Gannon C, Napolitano LM. Perioperative Anemia: An Independent Risk Factor for Infection, Mortality, and Resource Utilization in Surgery. 2001;102(2):237-244. Available from: http://www.idealibrary.com
27. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240(2):205–213. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15273542

Appendix

Appendix 1. Clavien-Dindo grading system for the classification of surgical complications

Grades	Definition of grade
Grade I	Any deviation from the normal perioperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. Allowed therapeutic regimes are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Normal course altered requiring pharmacological treatment other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anaesthesia
Grade IIIb	Intervention under general anaesthesia
Grade IV	Complications threatening the life of patients (including CNS complications) requiring ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
CNS, central nervous system, IC, intermediate care, ICU, intensive care unit	

[27]

Appendix 2 – HREC Documentation

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-enquiries@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

22 April 2020

HREC REF: 217/2020

Dr M Gibbs
Department of Anaesthesia & Perioperative Medicine
D-23 NGSH
Email: matthew.gibbs@uct.ac.za
Student: kathrynfidler@gmail.com

Dear Dr Gibbs

PROJECT TITLE: ANAEMIA IN A COLORECTAL ERAS PROGRAMME – IDENTIFYING THE PREVALENCE AND PREDICTORS OF PREOPERATIVE ANAEMIA AND THE EFFECT ON POSTOPERATIVE COMPLICATIONS AND LENGTH OF STAY -MMED CANDIDATE DR KATHRYN NIEUWENHUIS -SUB-STUDY LINKED TO R009-2015

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020.

Approval is granted for one year until the 30 April 2021.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr Kathryn Nieuwenhuis will also be involved in this study.

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	30.08.2022
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	5/8/2021

Note: Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za
Please clarify your plan for research-related activities during COVID-19 lockdown.
Please use the latest form found on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Comments to PI from the HREC
Thank you for the deviation document

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	02/08/2021		
HREC REF Number	217/2020	Current Ethics Approval was granted until	30 April 2021
Protocol title	Anaemia in a colorectal ERAS programme – identifying the prevalence and predictors of preoperative anaemia and the effect on postoperative complications and length of stay		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	√ **Yes**	R09-2015	

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)