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ORIGINAL RESEARCH

Small bowel capsule endoscopy for obscure gastrointestinal bleeding not associated with a reduction in iron or haemoglobin support

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Background: In obscure gastrointestinal bleeding (OGIB), capsule endoscopy has a high diagnostic yield, but its impact on clinically important outcomes such as rebleeding rates and transfusion requirements remains uncertain. This study aimed to investigate the effect of capsule endoscopy on red cell concentrate (RCC) transfusion and intravenous (IV) iron prescriptions in patients with OGIB.

Methods: We conducted a retrospective study and identified patients undergoing capsule endoscopy for OGIB from an endoscopy database at a tertiary teaching hospital. Data were collected on patient demographics, capsule findings, post-capsule invasive interventions, number of RCC units issued, IV iron prescriptions, and survival two years post-capsule. Data on RCC and IV iron were collected for a period of two years before and two years after capsule endoscopy for each patient. The primary outcome was comparison of RCC and IV iron quantities before and after capsule endoscopy. Secondary outcomes included the comparison of RCC and IV iron quantities based on the capsule result and the application of invasive interventions.

Results: Between January 2011 and December 2018, 96 patients who underwent capsule endoscopy for OGIB were enrolled, with a median age of 64.5 years (interquartile range [IQR] 35–80) and 57% (55/96) being female. Of the patients, 71 received RCC, with 337 units issued before the capsule (mean 4.7 units/patient) and 167 units issued post-capsule (mean 2.4 units/patient), representing a 49% decrease. Sixty-four patients received IV iron with 100 scripts before the capsule (mean 1.6/patient) and 140 scripts post-capsule (mean 2.2/patient), representing a 38% increase. During the post-capsule period, patients with a positive capsule received more RCC (2.7 vs. 1.9 units/patient) and more IV iron (2.3 vs. 1.9 scripts/patient) than those with a negative capsule; however, the differences were not statistically significant. Double balloon enteroscopy (DBE) was performed in 34% of patients (18/53) with a positive capsule, and the quantities of RCC and IV iron did not differ based on the application of this intervention. Patient survival at two years post-capsule was 92% (88/96).

Conclusion: In the two years after capsule endoscopy, RCC transfusions decreased by 49%, and IV iron scripts increased by 38%, suggesting an ongoing requirement for haemoglobin or iron level support.

Keywords: obscure gastrointestinal bleeding, capsule endoscopy, outcomes, transfusion, iron

Background

OGIB accounts for 10–20% of cases of gastrointestinal (GI) bleeding and is traditionally defined as bleeding of unknown origin that persists or recurs after negative initial bidirectional endoscopy evaluation.[1] The small bowel is the most common site of bleeding in these patients.[2] The endoscopic examination of the small bowel and investigation of OGIB was revolutionised with the advent of wireless capsule endoscopy.[3] Clinically significant lesions are diagnosed in 40–60% of small bowel capsule endoscopy procedures, with small bowel angiodysplasia being the most common lesion detected.[4-6] Not infrequently, capsule endoscopy also identifies clinically significant lesions outside the small bowel.[7]

Due to the obscure nature of bleeding and the often-benign underlying pathology, patients with OGIB tend to require repeated RCC transfusion or chronic iron replacement. Despite initial optimism, studies have observed that the improved diagnostic yield with capsule endoscopy may not necessarily translate into improved clinical outcomes in patients with OGIB. One randomised trial of 136 patients showed no significant differences in rebleeding rates, subsequent transfusions, or hospitalisations between patients undergoing capsule endoscopy versus dedicated small bowel contrast radiography after a 12-month observation period.[8] A retrospective study of capsule endoscopy in patients with iron deficiency showed a high rate of persisting anaemia in the long term in both positive and negative capsule patients, despite the former receiving a change in management.[9]

Despite the availability of capsule endoscopy in South Africa for many years, there is no published data on the yield or outcomes of this investigation. This retrospective study aimed to determine the impact of capsule endoscopy on RCC transfusions and IV iron prescriptions in patients with OGIB.

Methods

The study was conducted within the GI unit of a university teaching hospital in South Africa. Most capsule endoscopy referrals originate from medical and surgical departments within the hospital, with a smaller number referred from secondary-level health facilities in the province. We identified patients who

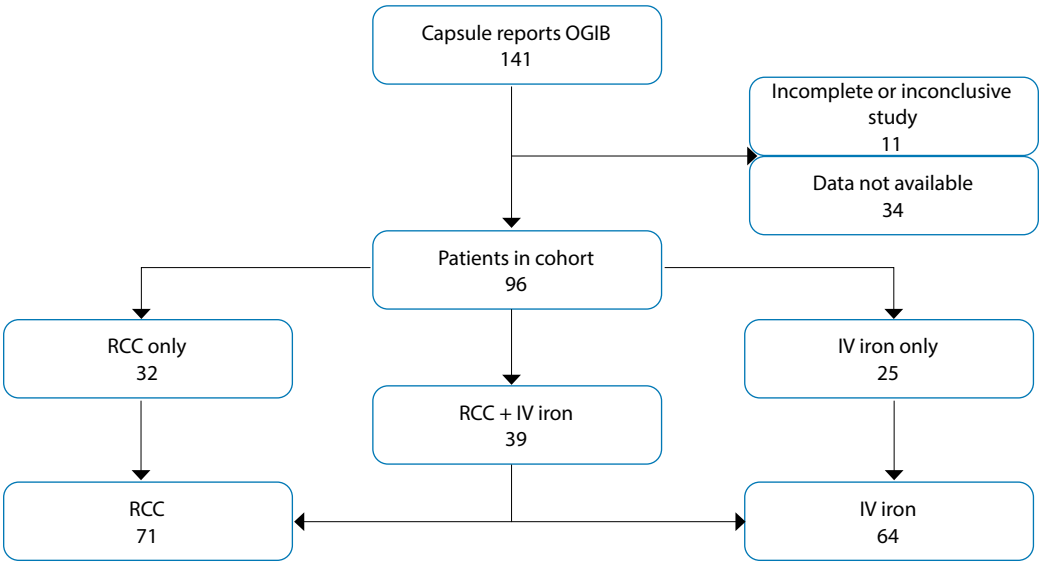

Figure 1: Flow chart for patient enrolment and stratification for analysis
IV – intravenous, OGIB – obscure gastrointestinal bleeding, RCC – red cell concentrate

underwent capsule endoscopy for OGIB between 2011 and 2018 from the capsule database. Small bowel capsule studies were performed using the PillCam™ software versions SB2 and SB3. Procedures and reports were done by local endoscopists who had undergone formal training in capsule endoscopy performance and interpretation. Data were obtained from the capsule reports regarding patient demographics, indication for the procedure, patient medical history, nature of OGIB (overt or occult), capsule endoscopy findings, and recommendations for further management. Patient folders were retrieved and reviewed to obtain information on interventions after capsule endoscopy.

Other interventions available were DBE, therapeutic angiography, and surgery. The Provincial Blood Service and the hospital pharmacy provided data on RCC transfusion and IV iron prescriptions, respectively. This was documented as the number of units of RCC issued per patient and the number of prescriptions of IV iron dispensed per patient. For each patient, data on RCC and IV iron were obtained for the period from two years before to two years after capsule endoscopy. Patients who had a capsule but did not have a record of receiving RCC or IV iron before or after their capsule procedure within the period of interest (two years before and after) were excluded from enrolment. RCC units and IV iron scripts were summated for the pre- and the post-capsule periods.

The primary outcome was a comparison of RCC and IV iron quantities before and after capsule endoscopy. Secondary outcomes included the comparison of these variables between patients with a positive and negative capsule and between patients who received and did not receive DBE. Figure 1 illustrates the derivation of the cohort studied and the stratification of data for analysis. The number of RCC units and IV iron scripts were analysed separately relative to the number of patients receiving the treatment.

Statistics

Non-normally distributed variables were expressed as the medians with IQRs and compared using the Mann–Whitney U test. Categorical variables were expressed as counts and percentages and compared with the chi-square or Fisher's exact tests. Statistical significance was established at $p < 0.05$ for all analyses. Data were analysed using Stata software version 11 (StataCorp LP, College Station, United States).

Results

From January 2011 to December 2018, 96 patients who underwent capsule endoscopy for OGIB and received RCC, IV iron, or both from two years before to two years after

Table I: Baseline characteristics of enrolled patients

Variable	*n* = 96	
Median age in years (IQR)	64.5 (35–80)	
	Number	%
Female	55	57
Occult bleeding	61	64
Overt bleeding	35	36
Comorbid cardiovascular disease*	21	22
Antiplatelet/anticoagulant use	16	17
Patients with positive capsule	53	55
Alive at 2 years post-capsule	88	92
Capsule findings in 53 patients with positive capsule result	**Number of patients with finding****	**%**
Angiodysplasia	30	57
Ulcer	9	17
Polyp/tumour	2	4
Blood with no overt lesion	6	11
Lesions outside small bowel	10	19
Patients receiving DBE	18	34

* Hypertension, ischaemic heart disease, valvular heart disease, or chronic kidney disease.
** Some patients had more than one abnormal finding.
DBE – double balloon enteroscopy, IQR – interquartile range

capsule endoscopy were enrolled. Table I shows the baseline characteristics of the enrolled patients.

Table II shows the number of RCC units and IV iron scripts before and after capsule endoscopy relative to the number of patients receiving the treatment. Among the 71 patients who received RCC, 337 units were transfused before and 167 units transfused post-capsule. With IV iron, the opposite was observed, where scripts increased from 100 before the capsule to 140 post-capsule in 64 patients.

Table II: Comparison of RCC and IV iron pre- and post-capsule

RCC		
RCC (*n* = 71)	**Units**	**Mean per patient**
Pre-capsule	337	4.7
Post-capsule	167	2.4
Change	**49% decrease**	
IV iron		
IV iron (*n* = 64)	**Scripts**	**Mean per patient**
Pre-capsule	100	1.6
Post-capsule	140	2.2
Change	**38% increase**	

IV – intravenous, RCC – red cell concentrate

Further analysis of the changes in RCC and IV iron according to whether the bleeding was overt or occult is shown in Table III. This analysis demonstrated that RCC transfusion decreased by 71% in patients presenting with overt bleeding and decreased by 36% in occult bleeders. IV iron scripts increased in approximately equal measure in overt (45%) and occult (41%) bleeding patients.

We compared RCC and IV iron quantities in the two years post-capsule between patients with positive and negative capsule results (Table IV). The comparison showed that patients with a positive capsule received more RCC and IV iron than those with

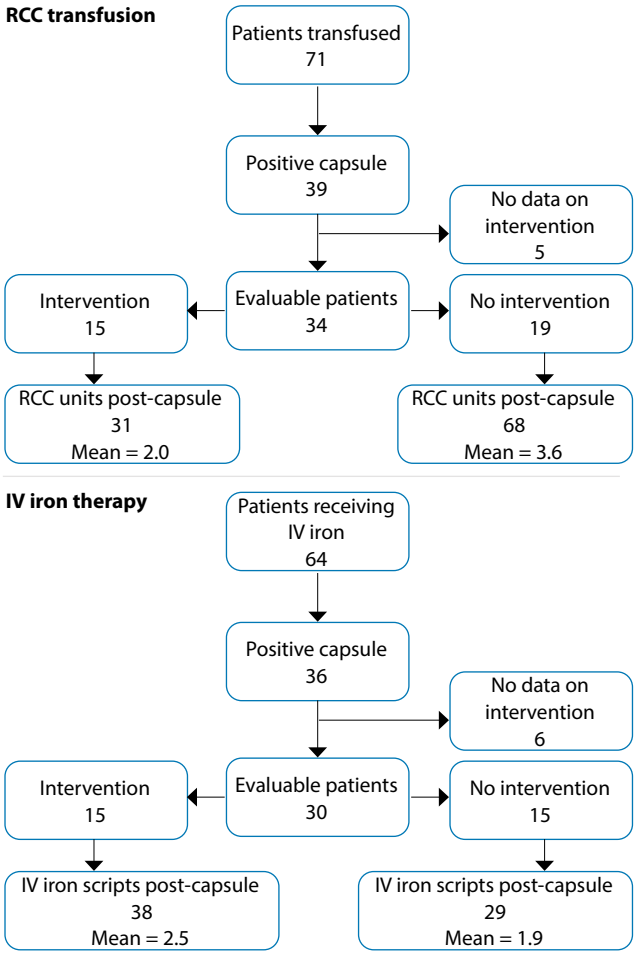

Figure 2: Post-capsule RCC and IV iron quantities based on intervention status among patients with a positive capsule
IV – intravenous, RCC – red cell concentrate

Table III: Relative decrease in RCC and increase in IV iron based on the nature of bleeding

RCC (*n* = 71)					
	Pre-capsule		**Post-capsule**		**Change**
Bleeding category	Units	Mean per patient	Units	Mean per patient	
Occult (*n* = 44)	205	4.7	130	3.0	36% decrease
Overt (*n* = 27)	132	4.9	37	1.4	71% decrease
IV iron (*n* = 64)					
	Pre-capsule		**Post-capsule**		**Change**
Bleeding category	Scripts	Mean per patient	Scripts	Mean per patient	
Occult (*n* = 47)	81	1.7	112	2.4	41% increase
Overt (*n* = 17)	19	1.1	28	1.6	45% increase

IV – intravenous, RCC – red cell concentrate

Table IV: RCC and IV iron quantities at two years post-capsule according to the capsule result

	Positive capsule (*n* = 39)		**Negative capsule (*n* = 32)**		***p*-value**
	Units	**Mean**	**Units**	**Mean**	
RCC	107	2.7	60	1.9	0.407
	Positive capsule (*n* = 36)		**Negative capsule (*n* = 28)**		***p*-value**
	Scripts	**Mean**	**Scripts**	**Mean**	
IV iron	82	2.3	52	1.9	0.675

IV – intravenous, RCC – red cell concentrate

a negative result. However, the differences were not statistically significant.

After capsule endoscopy, patients with a positive result were considered for further intervention depending on the nature of the lesion found and/or the degree of RCC or IV iron requirement. Most patients undergoing further intervention received DBE, with two patients undergoing open surgery. Figure 2 compares RCC and IV iron quantities in the post-capsule period based on whether further intervention was carried out.

Mean quantities of RCC were greater in the non-intervention group (3.6 vs. 2.0) but mean IV iron scripts were greater in the intervention group (2.5 vs. 1.9). The survival rate at two years post-capsule was 92%. Deaths were mostly attributable to chronic cardiovascular disease, such as chronic kidney disease.

Discussion

In the two years post-capsule, there was a decrease in RCC transfusions, accompanied by a comparable increase in IV iron prescriptions. This finding suggested an ongoing requirement for haemoglobin or iron level support in our cohort after capsule endoscopy. Further, no significant difference was observed in RCC and IV iron quantities between patients with positive and negative capsule results in the 2-year post-capsule follow up (Table IV). Studies with short follow-up periods (< 1 year) generally report a high negative predictive value for a negative capsule, with significantly less rebleeding in such patients.[10,11] However, longer-term follow-up (> 1–2 years), as in our study, may be associated with substantial rebleeding rates, even in patients with a negative capsule.[12]

The most common type of patient referred for capsule endoscopy for OGIB is the patient with occult bleeding and iron deficiency (64% in our study). Our study demonstrated a decrease in RCC transfusion (by 36%) and an increase in IV iron (by 41%) for this patient category in the post-capsule period. As highlighted earlier, this was suggestive of an ongoing and possibly similar requirement for supportive therapy, implying persisting or recurrent bleeding. It should be noted that, despite the ongoing need for iron or haemoglobin support, many patients were transitioned from RCC transfusion to IV iron-based support, which was a positive outcome resulting from capsule referral. The referral of patients to the GI unit for capsule endoscopy allowed them to be followed up and receive regular infusions in the IV iron clinic.

Patients with a positive or negative capsule did not differ in their requirements for RCC or IV iron in the post-capsule period. This suggests that negative capsule patients continued to bleed, and it raises the question of what management is available for patients after capsule endoscopy. In our study, DBE was performed in selected patients with a positive capsule, and the invasive intervention rate was 34% among patients with a positive capsule. Invasive intervention did not seem to make a difference in the quantities of RCC and IV iron between the intervention and non-intervention groups. A nationwide Korean study of 305 patients undergoing capsule endoscopy for OGIB reported a low intervention rate of 11.8% in patients with a positive capsule result, and that rebleeding rate, as in our study, did not differ by positive capsule result or the application of intervention treatment.[13]

An invasive intervention may not make a difference due to its selective application, generally low intervention rates, and the technical difficulties associated with applying endoscopic therapy in the small bowel. The adequacy of an invasive intervention, which is often used to treat angiodysplasia, is likely an important factor in influencing clinical outcomes. Although capsule endoscopy is a recommended and appropriate first-line investigation for OGIB,[14] it invariably reduces invasive intervention rates, especially when benign lesions such as angiodysplasia are diagnosed.

Study limitations

We acknowledge some limitations of our study. It was a retrospective study with some missing data. Consequently, 32% of potential participants were excluded from enrolment. A relatively small sample size of 96 patients was accrued, which may have affected the accuracy of the statistical analysis. We could not control for confounders such as variations in the management of iron deficiency or GI bleeding by different practitioners. We acknowledge the limitation of using RCC transfusion or iron infusion as indicators for recurrent GI bleeding, as some transfusions may be for anaemia due to other causes. However, we utilised transfusion records as best as possible to select transfusion events related to GI bleeding. We highlight that, despite the limitations noted above, our findings mirror results from similar studies in high-income countries. Moreover, to the best of our knowledge, this is the first study providing insights into the impact of capsule endoscopy in a low-resource, sub-Saharan African setting.

Conclusion

In this retrospective cohort study, we demonstrated an ongoing need for supportive care in the form of RCC and IV iron in patients with OGIB undergoing capsule endoscopy at a tertiary hospital in South Africa. However, we observed a transition of patients from RCC transfusion to IV iron-based support, which we consider a positive outcome.

Acknowledgements

The Provincial Blood Service provided data on RCC transfusions, and the head of the hospital pharmacy provided data on IV iron prescriptions. The GI unit clinical staff were part of the peer review process, and the unit administrative staff assisted with patient records for data collection.

Conflict of interest

The authors declare no conflict of interest.

Funding source

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Ethical approval

Before the study commenced, ethical approval was obtained from the Human Ethics and Research Committee of the University of Cape Town (reference number 280/2019). Permission to collect data was also obtained from the hospital administration and the Provincial Blood Service.

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