Adverse gastrointestinal bleeding associated with over-the-counter nonsteroidal anti-inflammatory drug use:

a cost study in two Gauteng public hospitals

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics worldwide. Unlike other classes of drugs, NSAIDs are increasingly available as an expanding range of over-the-counter (OTC) and prescription formulations. The mortality rate of individuals using chronic oral NSAIDs is one in five due to gastrointestinal complications. The economic implications to a challenged South African public healthcare system of treating serious, potentially preventable upper gastrointestinal bleeds attributed to the consumption of OTC NSAIDs does not appear to have been quantified.

Method: A prospective observational study was conducted at Chris Hani Baragwanath Academic Hospital and Charlotte Maxeke Johannesburg Academic Hospital over a six-month period.

Patients admitted to the surgical service with signs and symptoms of upper gastrointestinal bleeding were asked to complete a questionnaire-based survey. Clinical details were collected from patient files after they were discharged. The cost to treat each patient was calculated.

Results: Over the study period, 321 patients were admitted with upper gastrointestinal tract (UGIT) bleeding. The total cost to treat patients included in the study sample (n = 253) was R10 463 668. Patients using NSAIDs (n = 215) consumed 88% (R9 194 698) of the expenditure, seven times more than the cost of treating patients who did not use NSAIDs (n = 38; $p = 0.043$). Of the 215 patients who used NSAIDS, 183 had purchased over-the-counter NSAIDs and consumed 73% of the total expenditure.

Conclusion: Strict enforcement of existing regulations governing the distribution, sale and marketing of OTC NSAIDs as well as intensive consumer education of the adverse effects associated with NSAIDs usage are indicated in order to minimise the substantial financial cost to the public health system and morbidity to the South African population at risk.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used analgesics worldwide[1] and in contrast to other analgesic drug classes, are increasingly available as an expanding range of over-the-counter (OTC) and prescription formulations.[2] Currently there are 41 analgesic molecules available on the South African market in 738 different product formulations.[3]

The NSAIDs are perceived to be safe drugs by the general public and consequently OTC NSAID use is seven-times greater than that of prescribed NSAIDs.[4] However, NSAID use is associated with significant gastrointestinal tract complications. The aggregate risk of upper gastrointestinal tract (UGIT) complications among NSAID users is 2.7 to 5 times that of non-users.[5,6] A systematic review[7] of 61 067 cases investigated the mortality rate associated with UGIT bleeding or perforation. Data published since 1997 indicate that mortality is 1 in 13 overall but increases to 1 in 5 for patients exposed to NSAIDs.

In 2009, in an attempt to improve public awareness, the United States Food and Drug Administration issued a ruling requiring all NSAID manufacturers to list comprehensive warnings on all NSAID packaging with specific reference to UGIT bleeding, the most commonly reported adverse drug event in the country.[8]

Similar legislation does not exist in South Africa where non-selective NSAID preparations are readily available in pharmacies, grocery stores and a myriad of other formal and informal outlets with limited, if any, accompanying patient information. In the South African context, the direct financial implications to the public healthcare system of treating potentially preventable UGIT bleeding complications, attributed to the consumption of OTC NSAIDs, do not appear to have been quantified.

Methods

A prospective cohort study was conducted in the surgical wards of Chris Hani Baragwanath Academic Hospital (CHBAH) and Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)

over a six-month period. Ethics approval was obtained from the University of the Witwatersrand Human Research Ethics Committee (M110652). All study participants provided verbal informed consent. During the hospital admission, participants completed a written questionnaire with the assistance of a research nurse who was fluent in the commonly used languages. Assigning a study number to each questionnaire ensured patient confidentiality. Data collected included demographic information, medical history and details of analgesic use. On discharge, the relevant clinical, radiological, pharmacological, endoscopic and surgical information was collected from the patient's clinical notes in the hospital file.

Study population

The study population consisted of patients older than 12 years, admitted to the surgical wards during the study period with signs and symptoms of an acute UGIT bleed, confirmed by oesophagogastroduodenoscopy (OGD). The study sample included patients with pathology secondary to portal hypertension, Mallory-Weiss tears, oncological lesions, arteriovenous malformations, and incomplete questionnaires were excluded.

Data capture and analysis

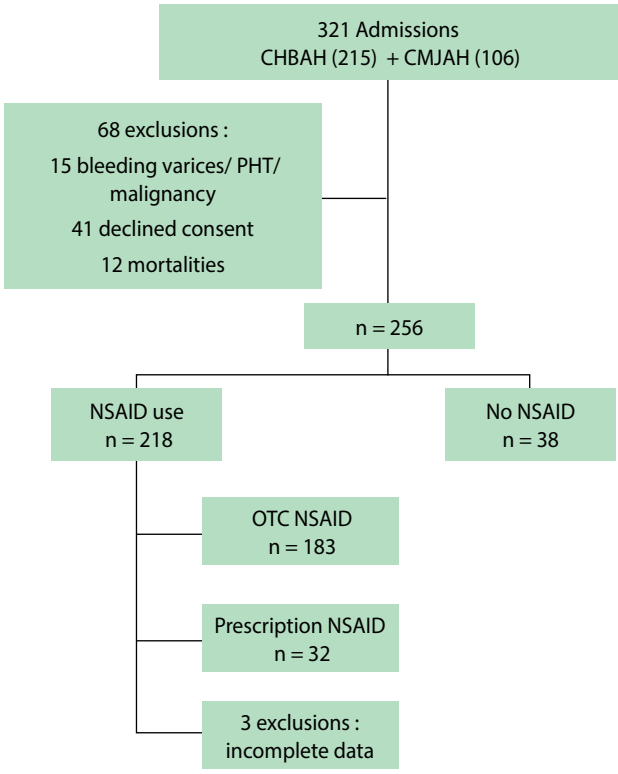
The data from both hospitals were combined and entered into a master Microsoft Excel spreadsheet. Patients were categorised based on their proclivity to use NSAIDs into two groups, 'NSAID' and 'no NSAID' use. Descriptive statistical analysis was performed on the demographic data and medical history. Subgroup analysis was performed for the patients who utilised NSAIDS as to the source of the NSAIDs as OTC or on prescription. SAS 9.3™ was used for statistical analyses. Where parametric t-Tests could not be used due to unequal variance, non-parametric Wilcoxon tests were used. Categorical data were compared using the Pearson's Chi Squared test.

UGIT bleed treatment cost calculation

The cost of UGIT bleeds was estimated by aggregating the cost of procedures performed to treat the UGIT bleed, medications, blood products and ward fees for each patient. The cost structure was based on unit costs of procedures, admissions, consultations, medications, blood products and imaging at a university-affiliated private sector hospital (Appendix 1) as the public sector costs were not easily obtainable. Expenditure on resuscitation measures, acute management and laboratory tests, as well as the use of disposable materials and equipment initiated in the emergency department and continued in the ward, were not included as the costs are assumed to be standardised for all patients in these hospitals.

Results

During the study period, 321 patients were admitted for treatment of an UGIT bleed, of which 68 were excluded from analysis as shown in Figure 1. Closer examination of the 68 exclusions, showed that there were twelve mortalities, of which five were unable to give consent (three were intubated and ventilated on arrival and two were in a state of confusion). The remaining seven patients all used OTC NSAIDs. The twelve patients were excluded from the cost analysis as all required prolonged organ support and multiple interventions that would have skewed the results. A further three patients who used NSAIDs were excluded as the details regarding OTC or prescription NSAID use were not clearly provided.



CHBAH Chris Hani Baragwanath Academic Hospital; CMJAH Charlotte Maxeke Johannesburg Academic Hospital; PHT portal hypertension; NSAID nonsteroidal anti-inflammatory; OTC over-the-counter

Figure 1. Study flow diagram

Table I illustrates the demographic and clinical characteristics of the study participants. Of the 256 participants, NSAID use was reported by the majority (85%) of the participants, with no NSAID use reported by only 38 of the participants. The average age was significantly different between the two groups indicating that a younger population used OTC NSAIDs.

Medical co-morbidities that demonstrated significant differences between the groups were hypertension, diabetes, arthritis and peptic ulcer disease. Patients were not asked specifically about any chronic medication that they used, other than analgesics.

The most common indication for OTC NSAID use in our population was headaches; musculoskeletal and abdominal pain followed. The majority of the population (% or n) surveyed did not require chronic analgesia on prescription for any of these common ailments.

Smoking and alcohol, in our population, were not significant in both groups of patients.

Table I. Demographic characteristics of NSAID users (n = 215). Values expressed as number (% of n = 215)

		NSAID use		
		OTC	Prescription	*p*-value
Demographics	Average age in years (range)	50 (14–87)	60 (19–88)	0.005
	Gender			
	Male	101 (47)	14 (6)	
	Female	83 (39)	18 (8)	
	Employment status Employed	59 (27)	5 (2)	
Social habits	Smoker	77 (36)	9 (4)	
	Alcohol	74 (34)	10 (5)	
Co-morbidities	Hypertension	58 (27)	21 (10)	0.0004
	Diabetes	18 8)	7 (3)	0.05
	HIV	20 (9)	2 (1)	
	Asthma	5 (2)	1 (0)	
	Arthritis	2 (1)	3 (1)	0.0004
	Peptic ulcer disease	41 (19)	13 (6)	0.04
	Other	7 (3)	3 (1)	
Indication for analgesia	Dental pain	6 (3)	0	
	Headache	79 (37)	4 (2)	0.001
	Musculoskeletal pain	62 (29)	15 (7)	
	Abdominal pain	35 (16)	9 (4)	
	Other	12 (6)	5 (2)	

Table II. Incidence of OTC NSAID analgesic by 183 participants. Values expressed as % of n =183 (number)

OTC NSAID usage based on analgesic class as named by patients	% of patients using OTC NSAIDs (number)
Grand-Pa™ (Aspirin-paracetamol-caffeine combination)	57.4% (105) NS
Paracetamol	34.4% (63) $p = 0.035$
Ibuprofen	8.7% (16) $p = 0.02$
Aspirin	32.8% (60) NS
Other NSAID and/or combination analgesics (paracetamol/codeine, paracetamol/ibuprofen, paracetamol/aspirin, paracetamol/ibuprofen/codeine, diclofenac and indomethacin)	32.8% (60) $p = 0.004$

NS – not significant

Table II provides details of the OTC NSAID usage patterns and includes data from patients using more than one type of OTC analgesic.

It is interesting to note, that in the population served by the public health system, no patient surveyed used a selective COX2 inhibitor. Patients named other NSAID combinations by the trade name the drug was sold as. MIMS prescribing guide[9] was used to confirm the constituents and the pharmacological name of the drug used. No-one obtained Grand-Pa™ on prescription. P values included compare the use of these medicines OTC and by prescription.

Table III examines the patterns of use of OTC and prescription NSAIDs. The results indicate that patients may take more medication more often than is recommended. The population surveyed was very brand-loyal. Only five percent of OTC NSAID users considered cost as a factor when purchasing analgesics. Patients indicated that they preferred to use brands they trusted, that had proven effect in the past and would reliably relieve their symptoms.

Although neither one of the results between the two groups was statistically significant, a minority of patients was aware of

Table III. Patterns of use of NSAIDs 215 respondents
Values represented as number (%)

		NSAID use		
		OTC	Prescription	*p*-value
Frequency of use	Daily	84 (39)	11 (5)	
	Twice daily	38 (18)	6 (3)	
	Thrice daily	37 (17)	16 (7)	0.0003
	Four times daily	5 (2)	1	
	> Four times daily	37 (17)	3 (1)	
Influenced by cost	Price	11 (5)	0	
No of tablets/dose	0.5	9 (4)	7 (3)	
	1	86 (40)	11 (5)	
	2	83 (38)	14 (7)	
	3	15 (7)	0	0.0007
	4	7 (3)	1	
	Other	14 (7)	1	
Instructions on use	Side-effects	23 (11)	4 (2)	
	Advice	14 (7)	5 (2)	
	Meals	114 (53)	22 (10)	
	Antacid	29 (13)	3 (1)	
	PPI	17 (8)	5 (2)	

p values indicate no statistical differences between the groups compared. SD: Standard Deviation. ICU: Intensive Care Unit (includes High Care). OGD: Oesophagogastroduodenoscopy, intervention includes any other method to treat visible ulceration or bleeding other than injection of normal saline or adrenaline

the side-effects of either type of drug. Fewer patients were given any advice when purchasing/collecting the NSAIDs. Fifty-three percent of patients surveyed (n = 215) took OTC NSAIDs with meals compared to 10% of the group taking prescription NSAIDs (n = 215). Very small numbers of patients concomitantly used an antacid or proton pump inhibitor.

Table IV outlines the details of the hospital admission. The relevant clinical information was collected from the hospital file after the patient was discharged. None of the parameters examined were statistically significant when the two groups were compared (Table IV). The findings suggest that the cost to treat upper gastrointestinal bleeds was comparable and was not influenced by the type of NSAID used by the patient. Costs were calculated using the cost structure in Appendix 1, where unit costs were multiplied by the number of days in hospital, invasive and non-invasive procedures and blood products consumed.

Data collection did include intravenous medications and radiological investigations. However these data were excluded in the table, as there was no difference in cost between the two groups.

The cost of treatment for all UGIT bleeds during the six-month period was R10 463 668 (n = 253). Patients using NSAIDs (n = 215) accounted for 88% (R9 194 698) of the cost. Of the patients who used NSAIDs, 85% (n = 183) obtained the NSAIDs as OTC medication and the treatment cost of R7 592 260, which amounted to 73% of the total expenditure.

The average cost to treat a patient with UGIT complications secondary to OTC vs Prescription NSAIDs was not statistically significant. Overall, due to the higher number of patients who used OTC NSAIDs, the cost incurred to treat these patients was five-fold more than to treat the patients taking prescription only NSAIDs.

Discussion

The South African Essential Medicines List (SA EML) proposes ibuprofen as an alternate analgesic to paracetamol in the first-line management of pain.[10] No alternative is suggested for ibuprofen, and consequently the use of NSAIDs is common in South Africa. This study was conducted in two tertiary hospitals in the public healthcare environment where patterns of OTC NSAID use and their relationship to UGIT bleeds have not previously been characterised.

During the study period, 70% (n = 215) of patients who were admitted with UGIT bleeds used NSAIDs, 85% (n = 183) of whom obtained their NSAIDs without a prescription. The incidence of OTC NSAID use was found to be far greater in the South African setting than in lower socioeconomic groups in first world countries, where 44% of patients admitted for UGIT haemorrhage used OTC NSAIDs.[4] The implication is that South African consumers, specifically in the lower socioeconomic groups, appear to obtain OTC NSAIDs easily but are not being provided with adequate information to guide their decision-making.

Table IV. Details of the hospital admission, in-hospital treatment and calculation of costs of NSAID vs non-NSAID users

	NSAID users			Non-NSAID users
	Total	OTC NSAID	Prescription OTC	
Number of participants	215	183	32	38
Age (years) Mean [Range (SD)]	51 [14–88 (18)]	50 [14–87 (17)]	60 [19–88 (21)]	46 [18–84 (20)]
Hospital admission Mean [Range (SD)]				
Length of stay (days)	6.3	6.23	6.5	5.74
	[2–54 (5)]	[2–54 (6)]	[2–30 (5)]	[2–16 (5)]
ICU length of stay (days)	0.3	0.29	0.13	0.11
	[0–19 (0.3)]	[0–19 (1.82)]	[0–2 (0.49)]	[0–4 (0.65)]
Endoscopy Mean [Range (SD)]				
OGD (n)	1	0.97	1.09	1
	[0–4 (0.7)]	[0–4 (0.7)]	[0–3 (0.69)]	[0–2 (0.57)]
Interventional OGD (n)	0.02	0.02	0.03	1
	[0–1 (0.15)]	[0–1 (0.15)]	[0–1 (0.18)]	[0–1 (0.23)]
Injection (n)	0.12	0.10	0.22	0
	[0–1 (0.32)]	[0–1 (0.3)]	[0–1 (0.42)]	
Surgery Mean [Range (SD)]				
Laparotomy (n)	0.11	0.11	0.09	0.08
	[0–1 (0.32)]	[0–1 (0.31)]	[0–1 (2.9)]	[0–1 (0.27)]
Relook laparotomy (n)	0.05	0.05	0	0
	[0–7 (0.49)]	[0–7 (0.53)]		
Blood products Mean [Range (SD)]				
Packed red cells (units)	1.96	1.94	1.66	1.61
	[0–17 (2.64)]	[0–15 (0.15)]	[0–7 (2.06)]	[0–9 (2.2)]
Fresh frozen plasma (units)	0.39	0.39	0.25	0
	[0–7(1.13)]	[0–7 (1.13)]	[0–4 (0.84)]	
Platelets (units)	0.05	0.04	0.06	0.03
	[0–2 (0.28)]	[0–2 (0.27)]	[0–2 (0.35)]	[0–1 (0.16)]
Subgroup cost	R9 194 698	R7 592 260	R1 602 438	R1 268 970
Total cost	**R10 463 668**			

In the current study, the three most significant risk factors for UGIT bleeds requiring hospital admission were advanced age, multiple medical co-morbidities and HIV infection, as indicated in Table I.

Age

Advanced age itself has been shown to be an independent risk factor for UGIT bleeding as well as the most widely reported risk factor for UGIT bleed-associated mortality.[11] Approximately 40–60% of NSAID consumers are over 60 years of age,[12] and up to 95% of elderly patients taking NSAIDs may obtain their medication OTC.[13] Of the individuals in the current study older than 60 years of age, 33% (n = 72) used NSAIDs of whom 79% (n = 57) obtained them OTC. In the Western world, the proportion of older patients suffering from UGIT bleeds has increased over recent years, mostly due to increased life expectancy and widespread NSAID use.[11] South Africa's population older than 60 years of age has increased from 2.8 million (1996) to 4.1 million (2011) with projections of 7 million by 2030. Current socio-economic assessments estimate that 40% of the elderly live in poverty, 38% rely on chronic medication and 28% have no formal education.[14] In view of the

fact that the risk of an UGIT bleed increases from 1.65 per 100 000 in patients < 65 years to 5.7 per 100 000 in those > 65 years and 12.7 per 100 000 in patients > 75 years of age[15,16] together with social and economic deficiencies, the potential cost to South Africa's healthcare is significant.

Co-morbidities

Epidemiological studies have demonstrated non-gastrointestinal co-morbidities as independent risk factors for UGIB.[17] This association was evident in the study participants taking OTC NSAIDs (Table III).

HIV

Pain is a common symptom in people living with HIV and AIDS, occurring in 60% to 98% of patients in South Africa.[18] The South African Essential Medicines List (SA EML) treatment protocol for management of adult HIV- and AIDS-related pain recommends paracetamol and/or ibuprofen as first-line treatment. A study conducted at a primary healthcare facility in the city of Tshwane determined that ibuprofen was prescribed for 44% of patients and aspirin, at analgesic doses, for 18%.[19] In addition, 84% of prescriptions contained suboptimal drug dosages and an insufficient quantity of tablets to sustain the patient to the next appointment, consequently more than 25% of the sample population used OTC analgesia.

In a study conducted at an HIV clinic in Houston Texas, OTC NSAIDs accounted for 38% of the most commonly used medications.[2] All of the patients taking NSAIDs were prescribed gastro-protective agents (GPAs) and the reported adverse drug reactions(ADR) with concurrent antiretroviral treatment was 16%, with most of the ADRs classified as type II drug reactions. In our study 22 patients volunteered their HIV status as positive and all of the 22 patients used NSAIDs, 20 as OTC NSAIDs and two as prescription NSAIDs. None of these patients took GPAs. GPAs are not listed in the SA EML . Approximately 6.4 million people in South Africa live with HIV,[20] consequently, the potential cost of NSAID-related UGIT bleeds in this population group is prodigious.

Economics

The cost of NSAID-induced gastropathy has been best quantified in the elderly, a population group that exhibits a high baseline rate of gastrointestinal bleeding,[21] as well as being the highest consumer group of NSAIDs.[22] Medical costs to treat the complications of UGIT bleeds in the elderly who use prescribed NSAIDs in the USA have been estimated at over $4 billion per year, and the annual cost attributed to lost work productivity and care exclusive of treatment expenditure amounts to $5.65 billion.[23] A limitation of these cohort healthcare cost studies is that OTC medication use is not included as these are paid for by the patient, hence these costs are not captured in clinical billing databases.

In South Africa more than 80% of the population do not have medical insurance, and studies have shown that many patients deem self-funded primary healthcare visits as expensive as well as inconvenient.[24] South African consumers have also been shown to perceive generic medicines, obtained at no cost from public healthcare providers, as inferior and of poor quality.[25] This places limitations on national medicine policies and may influence consumers to purchase specific, preferred brands of analgesics.

Self-medication is predicted to demonstrate a constant compound annual growth rate of 2% with ibuprofen expected to show amongst the strongest growth.[26] In 2009 pharmaceutical manufacturers updated and innovated their products to accommodate this expanding group of consumers. The current competitive South African analgesic market is dominated by a non-steroidal analgesic, Panado™ (paracetamol) with a brand retail value share of 34% (2013), an increase from 14% (2009). However, this is followed by several NSAID preparations including Grand-Pa™ (aspirin-paracetamol-caffeine) with 15% market share (2013) up from 13% (2009) and Disprin™ (aspirin) with 13% market share (2013) up from 8% (2009). These well-marketed brands are household names with a historical role in influencing customer choice, and are trusted and therefore widely available in both formal and informal retail settings as well as being supported by strong marketing campaigns.[26]

NSAID use in the South African public healthcare system does not mirror that of the private healthcare sector.[3] Selective cyclooxygenase-2 inhibitors are a group of NSAIDs which have a significantly lower incidence of UGIT side-effects. However, none of the surveyed population were prescribed these drugs (Table II). Proton-pump inhibitors were used by a meagre 8% and 2% in both the OTC- and prescription NSAID-use groups. Both drug classes are not included in the SA Primary Care EML.

Study limitations

Economic assessments to determine overall cost include evaluation of direct, indirect (productivity losses) and intangible (impaired quality of life) costs. Our study considered direct monetary costs hence it underestimates the actual cost to the individual as well as to society. We excluded the 12 patients that died during their admission, seven of whom were OTC NSAID users. Of the remaining five, we were unable to determine the extent of NSAID usage. This omission may further have underestimated the cost of NSAID-related complications.

NSAID use (including low dose aspirin) and *Helicobacter pylori* infection are among the most common independent risk factors for UGIB.[27] At the time of the study, CLO (*Campylobacter*-like organism) tests were not available during endoscopy hence the synergistic and additive effect of *H. pylori* infection with NSAIDs could not be assessed.

Lastly, this study was conducted in two of Gauteng's tertiary public hospitals. The population served by these hospitals may not fully represent the spectrum of NSAID use from all parts of the country.

Conclusion

NSAID use is common in South Africa and upper gastrointestinal tract bleeds resulting from OTC NSAID overuse are common,

potentially fatal and preventable. Patients are inadequately educated on the dangerous side-effects and do not self-administer these analgesics at correct dosages. The South African Medicines Control Council is incumbent to enforce the already existing legal parameters that require medication to be sold and distributed with correct, clear and concise labelling, a package insert and a straightforward patient information leaflet. Review of existing regulations of the sale, advertising and marketing of OTC NSAIDs in South Africa may decrease the risk of UGIT bleeds as well as reduce the substantial cost to the public healthcare system. Furthermore, GPAs have been proven to be cost-effective for the prophylaxis of UGIT bleeding in patients taking chronic non-selective NSAIDs. The cost of an annual prescription of 20 mg omeprazole per day is approximately R1 600 compared to approximately R41 000 for a single admission including a diagnostic endoscopy without surgery or special investigations to treat an NSAID-induced UGIT bleed. A recommendation would be that the existing 2014 SA EML be updated to include GPAs with NSAID use or include NSAID/GPA combination formulations.

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Appendix1

Treatment, investigation and procedural costs obtained from a university-affiliated hospital.

Estimated costs for 2013.

Currency: South African Rand (R)

Hospital cost per day	Initial consult with surgeon	R3 405
	Subsequent admission in a general ward	R2 905
	Intensive care unit admission – initial	R13 270
	Subsequent days in ICU	R11 270
	Ward admission cost	R6 409
Surgical interventions	Gastroscopy	R3 000
	Endoscopic injection with adrenaline	R100
	Biopsy of lesion	R100
	Sclerotherapy	R3 000
	Laparotomy – theatre time charged at 138.20/minute	R18 600
	Relook laparotomy – shorter duration of surgery assumed	R9 000
Blood products	Packed red cells	R5 000
	Platelets (mega unit)	R8 000
	Fresh frozen plasma	R4 800
Medication	Pantoprazole (intravenous)	R600
	Chest radiograph	R600
Radiology	Abdominal radiograph	R600
	Computerised tomogram	R2 000
	Abdominal ultrasound	R800