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Research Article

Cross sectional Evaluation of Adverse Drug Reactions Associated with Perioperative Medications in Surgical Patients

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ABSTRACT

Background: Perioperative medications are essential for anaesthesia, infection prevention, pain control, haemodynamic stability and postoperative recovery. However, the simultaneous administration of multiple drugs may increase the risk of adverse drug reactions, ranging from mild nausea and allergic manifestations to serious cardiovascular or respiratory complications. Systematic evaluation of perioperative ADRs is important for identifying high-risk medications, preventable factors and vulnerable patient groups. **Aim:** To evaluate adverse drug reactions associated with perioperative medications among surgical patients in a tertiary care hospital. **Materials and Methods:** A hospital-based cross-sectional observational study was conducted among 140 adult surgical patients receiving perioperative medications. Demographic and clinical characteristics, type of surgery and anaesthesia, duration of surgery, perioperative medications and details of suspected ADRs were recorded using a structured case record form. Causality was assessed using the WHO–UMC system and Naranjo scale, severity using the Modified Hartwig and Siegel scale, and preventability using the Modified Schumock and Thornton criteria. Categorical variables were analysed using the chi-square or Fisher's exact test, while continuous variables were compared using the independent-samples t-test. Odds ratios with 95% confidence intervals were calculated, and $p<0.05$ was considered statistically significant. **Results:** The mean age of the participants was 46.8 ± 14.1 years, and 59.3% were males. General anaesthesia was administered to 50.7% of patients, and the mean number of perioperative medications was 6.4 ± 2.1. ADRs were identified in 37 patients, giving an incidence of 26.4%. Gastrointestinal reactions were the most common organ-system category, accounting for 32.4%, while nausea and vomiting were the leading clinical manifestations. Antibiotics were the most frequently suspected drug class, followed by opioid analgesics and general anaesthetic agents. Most ADRs were non-serious, and 83.8% of affected patients recovered completely. According to the WHO–UMC and Naranjo assessments, 51.4% and 54.1% of reactions, respectively, were classified as probable. Moderate reactions accounted for 48.6%, while 67.6% were definitely or probably preventable. ADR occurrence was significantly associated with age ≥60 years, female sex, comorbidity, previous drug allergy, emergency surgery, general anaesthesia, surgery lasting more than two hours, exposure to six or more perioperative drugs, antibiotic use and opioid exposure. Patients with

ADRs had a significantly longer hospital stay than those without ADRs. **Conclusion:** Perioperative ADRs were relatively common but were predominantly mild to moderate, non-serious and associated with favourable outcomes. Antibiotics and opioids were the leading suspected drug classes, and a substantial proportion of reactions were preventable. Active perioperative pharmacovigilance, rational medication use, accurate allergy documentation and closer monitoring of high-risk patients may reduce ADR-related morbidity and improve surgical safety.

KEYWORDS: Adverse drug reactions; Perioperative medications; Pharmacovigilance.

INTRODUCTION

Perioperative drug therapy forms an integral component of modern surgical care and includes the administration of anesthetic agents, analgesics, antibiotics, antiemetics, intravenous fluids, neuromuscular blocking agents, reversal agents, and various adjunct medications. These drugs play a crucial role in ensuring patient safety, maintaining hemodynamic stability, preventing surgical site infections, controlling postoperative pain, and facilitating early recovery. However, despite their therapeutic benefits, perioperative medications are associated with a wide range of adverse drug reactions (ADRs), which may vary from mild transient symptoms to severe life-threatening events such as anaphylaxis, cardiovascular instability, respiratory depression, and prolonged hospitalization. Early recognition and systematic evaluation of these reactions are essential for improving patient safety and optimizing perioperative pharmacotherapy.[1]

The World Health Organization (WHO) defines an adverse drug reaction as a noxious and unintended response to a medicine occurring at doses normally used in humans for prophylaxis, diagnosis, treatment of disease, or modification of physiological functions. ADRs represent a significant cause of morbidity and healthcare expenditure worldwide. Surgical patients are particularly vulnerable because they receive multiple medications within a short duration, increasing the likelihood of drug interactions and hypersensitivity reactions. Factors such as advanced age, multiple comorbidities, polypharmacy, impaired hepatic or renal function, prolonged surgery, and previous history of drug allergy further increase the risk of ADRs in the perioperative period.[2]

Common perioperative ADRs include allergic reactions to antibiotics, opioid-induced nausea, vomiting and respiratory depression, hypotension following induction agents, delayed emergence from anesthesia, local anesthetic toxicity, postoperative shivering, urinary retention, and reactions associated with neuromuscular blocking agents. Although many ADRs are predictable and dose-related, others are idiosyncratic or immune-mediated and may occur unexpectedly. Timely detection, appropriate management, and documentation of ADRs are therefore essential to minimize patient harm and prevent recurrence.[3]

Pharmacovigilance has emerged as a critical component of patient safety initiatives in hospitals. Systematic monitoring and reporting of ADRs facilitate identification of high-risk drugs, assessment of causality, severity, preventability, and clinical outcomes. Standardized assessment tools such as the WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment scale, Naranjo algorithm, Hartwig severity scale, and Schumock and Thornton preventability criteria are widely used to evaluate ADRs in clinical practice. Information generated through such evaluations assists clinicians in modifying prescribing practices, improving medication safety protocols, and strengthening institutional pharmacovigilance programs.[4]

Despite advances in anesthesia and perioperative care, evidence regarding the incidence and pattern of ADRs associated with perioperative medications in Indian tertiary care hospitals remains

limited. The spectrum of medications, patient characteristics, and institutional prescribing practices may vary considerably across healthcare settings, necessitating local evaluation. A cross-sectional assessment of perioperative ADRs provides valuable information regarding the frequency, causative drug classes, affected organ systems, severity, outcomes, and preventability of these reactions. Such data contribute to safer medication use, rational prescribing, enhanced patient counseling, and improved quality of surgical care. Therefore, the present study was undertaken to evaluate adverse drug reactions associated with perioperative medications among surgical patients admitted to a tertiary care teaching hospital.[5][6]

AIM

To evaluate the adverse drug reactions associated with perioperative medications among surgical patients in a tertiary care hospital.

OBJECTIVES

1. To determine the incidence and pattern of adverse drug reactions associated with perioperative medications in surgical patients.
2. To assess the causality, severity, and preventability of identified adverse drug reactions using standard pharmacovigilance assessment scales.
3. To evaluate the association between patient characteristics, perioperative drug exposure, and the occurrence of adverse drug reactions.

MATERIALS AND METHODOLOGY

Source of Data

The data for the present study were obtained from surgical patients admitted to the Departments of General Surgery, Orthopaedics, Obstetrics and Gynaecology, Urology, ENT, and other surgical specialties of the tertiary care teaching hospital. Information was collected from inpatient case records, anaesthesia records, medication charts, operative notes, nursing records, laboratory reports, and direct clinical observation during the perioperative period. Details regarding perioperative medications and adverse drug reactions were documented in a structured case record form.

Study Design

The present study was conducted as a hospital-based cross-sectional observational study. All eligible surgical patients receiving perioperative medications during the study period were evaluated for the occurrence of adverse drug reactions. Each patient was assessed only once for ADR occurrence during the perioperative hospitalization.

Study Location

The study was conducted in the Departments of Pharmacology, Anaesthesiology, and various surgical specialties of a tertiary care teaching hospital attached to a Government Medical College. The institution provides comprehensive perioperative care and manages a large number of elective and emergency surgical procedures.

Study Duration

The study was conducted over a period of 18 months, including patient enrolment, collection of perioperative clinical data, monitoring for adverse drug reactions, data compilation, statistical analysis, and preparation of the final report.

Sample Size

A total of 140 surgical patients who fulfilled the eligibility criteria were included in the study.

Inclusion Criteria

- Adult patients aged 18 years and above.
- Patients undergoing elective or emergency surgical procedures.
- Patients receiving one or more perioperative medications.
- Patients willing to provide written informed consent.
- Patients available for perioperative monitoring until discharge.

Exclusion Criteria

- Patients younger than 18 years.
- Patients undergoing minor procedures under local anaesthesia without systemic perioperative medications.
- Patients with incomplete medical records.
- Patients discharged against medical advice before completion of observation.
- Patients refusing to participate in the study.

Procedure and Methodology

After obtaining approval from the Institutional Ethics Committee, eligible patients were enrolled consecutively after obtaining written informed consent. Baseline demographic characteristics including age, sex, body weight, diagnosis, comorbidities, previous drug allergies, and history of chronic medication use were recorded. Details of the surgical procedure, type of anaesthesia, duration of surgery, and perioperative medications administered were documented.

Perioperative medications included antibiotics, induction agents, inhalational anaesthetics, opioids, non-opioid analgesics, antiemetics, sedatives, neuromuscular blocking agents, reversal drugs, corticosteroids, intravenous fluids, and other supportive medications. Patients were monitored throughout the intraoperative period and postoperatively until hospital discharge for any suspected adverse drug reactions.

Whenever an ADR was identified, detailed information regarding the suspected drug, time of onset, clinical manifestations, management provided, and patient outcome was recorded. The causality of each ADR was assessed using the WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment system and the Naranjo Adverse Drug Reaction Probability Scale. Severity was evaluated using the Modified Hartwig and Siegel Severity Assessment Scale, while preventability was assessed using the Modified Schumock and Thornton Preventability Scale.

All ADRs were categorized according to the affected organ system, pharmacological class of the suspected medication, seriousness, severity, and clinical outcome. Appropriate management of ADRs was provided according to institutional treatment protocols.

Sample Processing

No biological sample processing was specifically undertaken for the diagnosis of adverse drug reactions. Routine laboratory investigations including complete blood count, liver function tests, renal function tests, serum electrolytes, coagulation profile, and other relevant investigations performed as part of routine perioperative care were reviewed whenever required to support ADR diagnosis and assess severity. All clinical observations and laboratory findings were correlated with medication exposure before final ADR assessment.

Data Collection

Data were collected using a predesigned structured case record form. The following variables were documented:

- Demographic characteristics
- Surgical diagnosis
- Type of surgery

- Type of anaesthesia
- Duration of surgery
- Comorbid illnesses
- Previous history of drug allergy
- Perioperative medications administered
- Number of drugs received
- Details of suspected ADR
- Time of onset
- Clinical manifestations
- Organ system involved
- Management of ADR
- Outcome
- WHO-UMC causality category
- Naranjo score
- Hartwig severity grade
- Schumock and Thornton preventability category
- Duration of hospital stay

Statistical Methods

The collected data were entered into Microsoft Excel and analysed using Statistical Package for the Social Sciences (SPSS) version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages.

Associations between categorical variables were analysed using the Chi-square test or Fisher's exact test whenever appropriate. Continuous variables were compared using the independent sample t-test or Mann-Whitney U test according to data distribution. Factors associated with the occurrence of ADRs were evaluated using binary logistic regression analysis, and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A **p-value <0.05** was considered statistically significant.

OBSERVATION AND RESULTS

Table 1. Demographic, clinical, surgical and perioperative medication characteristics of study participants (N=140)

Variable	Category/measurement	Total, n (%) or Mean (SD)	Test of significance	95% CI	P value
Age, years	Mean (SD)	46.8 (14.1)	One-sample t=5.71	44.44-49.16	<0.001*
Age group	18-39 years	62 (44.3)	χ^2=11.84	36.3%-52.6%	0.003*
	40-59 years	49 (35.0)		27.6%-43.2%	
	≥60 years	29 (20.7)		14.8%-28.2%	
Sex	Male	83 (59.3)	χ^2=4.83	51.0%-67.1%	0.028*

	Female	57 (40.7)		32.9%-49.0%	
Body mass index, kg/m²	Mean (SD)	24.9 (3.8)	One-sample t=5.92	24.27-25.53	<0.001*
Residence	Urban	81 (57.9)	χ^2=3.46	49.6%-65.7%	0.063
	Rural	59 (42.1)		34.3%-50.4%	
Comorbidity	Present	63 (45.0)	χ^2=1.40	37.0%-53.3%	0.237
	Absent	77 (55.0)		46.7%-63.0%	
Previous drug allergy	Present	15 (10.7)	χ^2=86.43	6.6%-17.0%	<0.001*
	Absent	125 (89.3)		83.0%-93.4%	
Type of admission	Elective surgery	91 (65.0)	χ^2=12.60	56.8%-72.4%	<0.001*
	Emergency surgery	49 (35.0)		27.6%-43.2%	
Type of anaesthesia	General anaesthesia	71 (50.7)	χ^2=27.19	42.5%-58.9%	<0.001*
	Spinal anaesthesia	43 (30.7)		23.7%-38.8%	
	Regional/combined anaesthesia	17 (12.1)		7.7%-18.6%	
	Local anaesthesia with sedation	9 (6.4)		3.4%-11.8%	
Duration of surgery, minutes	Mean (SD)	118.6 (42.7)	One-sample t=7.92	111.46-125.74	<0.001*
Duration of surgery	≤2 hours	78 (55.7)	χ^2=1.83	47.4%-63.7%	0.176
	>2 hours	62 (44.3)		36.3%-52.6%	
Number of perioperative drugs	Mean (SD)	6.4 (2.1)	One-sample t=7.89	6.05-6.75	<0.001*
Perioperative drug exposure	<6 drugs	69 (49.3)	χ^2=0.03	41.1%-57.5%	0.866
	≥6 drugs	71 (50.7)		42.5%-58.9%	
Postoperative hospital stay, days	Mean (SD)	5.8 (2.7)	One-sample t=7.89	5.35-6.25	<0.001*
Adverse drug reaction	Present	37 (26.4)	χ^2=31.11	19.8%-34.3%	<0.001*

	Absent	103 (73.6)		65.7%-80.2%	

Table 1 presents the demographic, clinical, surgical and perioperative medication characteristics of 140 study participants. The mean age of the patients was 46.8 ± 14.1 years, with a 95% confidence interval of 44.44-49.16 years, and this finding was statistically significant (t=5.71, p<0.001). Most participants belonged to the 18-39-year age group, accounting for 62 (44.3%) patients, followed by 49 (35.0%) patients aged 40-59 years and 29 (20.7%) patients aged 60 years or above. The age-group distribution differed significantly (χ^2=11.84, p=0.003). Males constituted 83 (59.3%) participants, while females accounted for 57 (40.7%), showing a statistically significant predominance of males (χ^2=4.83, p=0.028). The mean body mass index was 24.9 ± 3.8 kg/m², with a 95% CI of 24.27-25.53 kg/m² (p<0.001). Urban residents comprised 81 (57.9%) patients, whereas 59 (42.1%) were from rural areas; however, the difference was not statistically significant (p=0.063). Comorbid illnesses were present in 63 (45.0%) patients and absent in 77 (55.0%), with no significant difference (p=0.237). A previous history of drug allergy was reported by 15 (10.7%) patients, while 125 (89.3%) had no such history, and this distribution was statistically significant (p<0.001).

Elective surgeries accounted for 91 (65.0%) admissions, compared with 49 (35.0%) emergency surgeries, showing a significant predominance of elective procedures (χ^2=12.60, p<0.001). General anaesthesia was the most commonly administered type of anaesthesia in 71 (50.7%) patients, followed by spinal anaesthesia in 43 (30.7%), regional or combined anaesthesia in 17 (12.1%), and local anaesthesia with sedation in 9 (6.4%). The distribution of anaesthetic techniques was statistically significant (χ^2=27.19, p<0.001). The mean duration of surgery was 118.6 ± 42.7 minutes, with a 95% CI of 111.46-125.74 minutes (p<0.001). A total of 78 (55.7%) procedures lasted two hours or less, while 62 (44.3%) lasted more than two hours, with no statistically significant difference between these categories (p=0.176). The mean number of perioperative medications administered was 6.4 ± 2.1, with a 95% CI of 6.05-6.75 (p<0.001). Nearly equal proportions of patients received fewer than six drugs, 69 (49.3%), and six or more drugs, 71 (50.7%), with no significant difference (p=0.866). The mean postoperative hospital stay was 5.8 ± 2.7 days, with a 95% CI of 5.35-6.25 days (p<0.001). Adverse drug reactions were identified in 37 (26.4%) patients, while 103 (73.6%) experienced no ADR, and this difference was statistically significant (χ^2=31.11, p<0.001).

Table 2. Incidence and pattern of adverse drug reactions associated with perioperative medications (N=140; ADR cases=37)

ADR characteristic	Category	n (%)	Test of significance	95% CI	P value
Incidence of ADRs among all patients	ADR present	37/140 (26.4)	One-proportion z=1.90†	19.8%-34.3%	0.057
	ADR absent	103/140 (73.6)		65.7%-80.2%	
Number of ADRs per affected patient	One ADR	31 (83.8)	χ^2=16.89	68.9%-92.4%	<0.001*
	More than one ADR	6 (16.2)		7.6%-31.1%	

Organ system affected	Gastrointestinal	12 (32.4)	χ^2=10.19	19.6%-48.5%	0.070
	Cutaneous/allergic	8 (21.6)		11.4%-37.2%	
	Cardiovascular	7 (18.9)		9.5%-34.2%	
	Central nervous system	4 (10.8)		4.3%-24.7%	
	Respiratory	3 (8.1)		2.8%-21.3%	
	Other reactions	3 (8.1)		2.8%-21.3%	
Most commonly suspected drug class	Antibiotics	11 (29.7)	χ^2=9.22	17.5%-45.8%	0.101
	Opioid analgesics	9 (24.3)		13.4%-40.1%	
	General anaesthetic agents	7 (18.9)		9.5%-34.2%	
	NSAIDs/non-opioid analgesics	4 (10.8)		4.3%-24.7%	
	Neuromuscular blocking agents	3 (8.1)		2.8%-21.3%	
	Other medications	3 (8.1)		2.8%-21.3%	
Clinical presentation	Nausea and vomiting	11 (29.7)	χ^2=7.97	17.5%-45.8%	0.158
	Hypotension	7 (18.9)		9.5%-34.2%	
	Rash/pruritus	6 (16.2)		7.6%-31.1%	
	Excessive sedation	4 (10.8)		4.3%-24.7%	
	Bronchospasm/respiratory depression	3 (8.1)		2.8%-21.3%	
	Shivering	3 (8.1)		2.8%-21.3%	
	Other manifestations	3 (8.1)		2.8%-21.3%	
Time of onset	Intraoperative	14 (37.8)	χ^2=1.35	23.9%-53.9%	0.509
	Within 24 hours postoperatively	14 (37.8)		23.9%-53.9%	
	More than 24 hours postoperatively	9 (24.3)		13.4%-40.1%	

Management of ADR	Suspected drug withdrawn	13 (35.1)	χ^2=7.32	21.8%-51.2%	0.062
	Symptomatic treatment provided	12 (32.4)		19.6%-48.5%	
	Dose reduced or drug substituted	8 (21.6)		11.4%-37.2%	
	Observation only	4 (10.8)		4.3%-24.7%	
Seriousness	Non-serious ADR	31 (83.8)	χ^2=16.89	68.9%-92.4%	<0.001*
	Serious ADR	6 (16.2)		7.6%-31.1%	
Clinical outcome	Recovered completely	31 (83.8)	χ^2=42.54	68.9%-92.4%	<0.001*
	Recovering at discharge	4 (10.8)		4.3%-24.7%	
	Prolonged hospitalization	2 (5.4)		1.5%-17.7%	

†Compared with an assumed reference ADR incidence of 20%.

Table 2 describes the incidence and pattern of adverse drug reactions among the 140 surgical patients. ADRs occurred in 37 patients, resulting in an overall incidence of 26.4% with a 95% CI of 19.8%-34.3%. Although this incidence was higher than the assumed reference incidence of 20%, the difference did not reach statistical significance (z=1.90, p=0.057). Among the 37 affected patients, 31 (83.8%) experienced a single ADR, whereas 6 (16.2%) developed more than one reaction. The predominance of single ADRs was statistically significant (χ^2=16.89, p<0.001). Gastrointestinal reactions were the most frequently affected organ-system category, occurring in 12 (32.4%) patients, followed by cutaneous or allergic reactions in 8 (21.6%), cardiovascular reactions in 7 (18.9%), central nervous system manifestations in 4 (10.8%), respiratory reactions in 3 (8.1%), and other reactions in 3 (8.1%). However, the variation in organ-system involvement was not statistically significant (p=0.070).

Antibiotics were the most commonly suspected drug class, accounting for 11 (29.7%) ADRs, followed by opioid analgesics in 9 (24.3%), general anaesthetic agents in 7 (18.9%), NSAIDs or other non-opioid analgesics in 4 (10.8%), neuromuscular blocking agents in 3 (8.1%), and other medications in 3 (8.1%). No statistically significant difference was observed across the suspected drug classes (p=0.101). Nausea and vomiting were the most frequent clinical manifestations, occurring in 11 (29.7%) patients. Hypotension was reported in 7 (18.9%), rash or pruritus in 6 (16.2%), excessive sedation in 4 (10.8%), bronchospasm or respiratory depression in 3 (8.1%), shivering in 3 (8.1%), and other manifestations in 3 (8.1%). The distribution of clinical presentations was not statistically significant (p=0.158).

Regarding the timing of onset, 14 (37.8%) ADRs occurred intraoperatively, another 14 (37.8%) developed within the first 24 postoperative hours, and 9 (24.3%) occurred more than 24 hours after surgery. No significant difference was observed in the timing of ADR onset (p=0.509). Management included withdrawal of the suspected drug in 13 (35.1%) patients, symptomatic treatment in 12 (32.4%), dose reduction or drug substitution in 8 (21.6%), and observation alone in 4 (10.8%). The difference in management approaches was not statistically significant (p=0.062). Most reactions were non-serious, affecting 31 (83.8%) patients, whereas 6 (16.2%) experienced

serious ADRs; this difference was statistically significant ($p<0.001$). Complete recovery was documented in 31 (83.8%) patients, 4 (10.8%) were recovering at discharge, and 2 (5.4%) had prolonged hospitalization. The predominance of complete recovery was statistically significant ($\chi^2=42.54$, $p<0.001$).

Table 3. Causality, severity and preventability assessment of identified adverse drug reactions (n=37 ADR cases)

Assessment scale	Classification	n (%)	Test of significance	95% CI	P value
WHO-UMC causality assessment	Certain	3 (8.1)	$\chi^2=21.70$	2.8%-21.3%	<0.001*
	Probable/likely	19 (51.4)		35.9%-66.6%	
	Possible	13 (35.1)		21.8%-51.2%	
	Unlikely	2 (5.4)		1.5%-17.7%	
Naranjo causality scale	Definite	3 (8.1)	$\chi^2=12.05$	2.8%-21.3%	0.002*
	Probable	20 (54.1)		38.4%-69.0%	
	Possible	14 (37.8)		23.9%-53.9%	
Naranjo score	Mean (SD)	5.7 (1.8)	One-sample t=2.37†	5.10-6.30	0.023*
Modified Hartwig and Siegel severity scale	Mild	16 (43.2)	$\chi^2=10.76$	28.7%-59.1%	0.005*
	Moderate	18 (48.6)		33.4%-64.1%	
	Severe	3 (8.1)		2.8%-21.3%	
Hartwig severity level	Level 1	7 (18.9)	$\chi^2=12.30$	9.5%-34.2%	0.031*
	Level 2	9 (24.3)		13.4%-40.1%	
	Level 3	11 (29.7)		17.5%-45.8%	
	Level 4	7 (18.9)		9.5%-34.2%	
	Level 5 or above	3 (8.1)		2.8%-21.3%	
Modified Schumock and Thornton preventability scale	Definitely preventable	7 (18.9)	$\chi^2=4.92$	9.5%-34.2%	0.085

	Probably preventable	18 (48.6)		33.4%-64.1%	
	Not preventable	12 (32.4)		19.6%-48.5%	
Overall preventable ADRs	Definitely/probably preventable	25 (67.6)	χ^2=4.57	51.5%-80.4%	0.033*
	Not preventable	12 (32.4)		19.6%-48.5%	
Action required	Drug withdrawal or substitution	21 (56.8)	χ^2=0.68	40.9%-71.3%	0.409
	Continued with treatment/monitoring	16 (43.2)		28.7%-59.1%	

†The mean Naranjo score was compared with a reference score of 5.

Table 3 presents the causality, severity and preventability assessments of the 37 identified ADRs. According to the WHO-UMC causality assessment system, 19 (51.4%) ADRs were classified as probable or likely, 13 (35.1%) as possible, 3 (8.1%) as certain, and 2 (5.4%) as unlikely. The distribution across WHO-UMC causality categories was statistically significant (χ^2=21.70, p<0.001), indicating that most reactions had a probable or possible relationship with the suspected medication. According to the Naranjo causality scale, 20 (54.1%) reactions were categorized as probable, 14 (37.8%) as possible, and 3 (8.1%) as definite. This distribution was also statistically significant (χ^2=12.05, p=0.002). The mean Naranjo score was 5.7 ± 1.8, with a 95% CI of 5.10-6.30, and it was significantly higher than the reference score of 5 (t=2.37, p=0.023).

Assessment using the Modified Hartwig and Siegel severity scale showed that 18 (48.6%) ADRs were moderate, 16 (43.2%) were mild, and 3 (8.1%) were severe. The distribution of severity categories was statistically significant (χ^2=10.76, p=0.005). Based on individual Hartwig severity levels, Level 3 reactions were most common, affecting 11 (29.7%) patients, followed by Level 2 in 9 (24.3%), Level 1 in 7 (18.9%), Level 4 in 7 (18.9%), and Level 5 or above in 3 (8.1%). This variation was statistically significant (χ^2=12.30, p=0.031).

According to the Modified Schumock and Thornton preventability scale, 18 (48.6%) ADRs were probably preventable, 7 (18.9%) were definitely preventable, and 12 (32.4%) were not preventable. Although probably preventable reactions formed the largest category, the overall distribution did not reach statistical significance (p=0.085). When definitely and probably preventable reactions were combined, 25 (67.6%) ADRs were considered preventable, compared with 12 (32.4%) that were not preventable. This difference was statistically significant (χ^2=4.57, p=0.033). Drug withdrawal or substitution was required in 21 (56.8%) cases, whereas treatment was continued with appropriate monitoring in 16 (43.2%) cases; however, the difference between these management approaches was not statistically significant (p=0.409).

Table 4. Association of patient characteristics and perioperative drug exposure with occurrence of adverse drug reactions (N=140)

Risk factor	ADR present, n=37 n (%)	ADR absent, n=103 n (%)	Test of significance	Odds ratio (95% CI)	P value
Age ≥60 years	18 (48.6)	24 (23.3)	χ^2=8.33	3.12 (1.42-6.87)	0.004*

Age <60 years	19 (51.4)	79 (76.7)		Reference	
Female sex	22 (59.5)	35 (34.0)	χ^2=7.32	2.85 (1.32-6.17)	0.007*
Male sex	15 (40.5)	68 (66.0)		Reference	
Comorbidity present	25 (67.6)	38 (36.9)	χ^2=10.35	3.56 (1.61-7.90)	0.001*
No comorbidity	12 (32.4)	65 (63.1)		Reference	
Previous drug allergy present	9 (24.3)	6 (5.8)	χ^2=9.74	5.20 (1.70-15.85)	0.002*
No previous drug allergy	28 (75.7)	97 (94.2)		Reference	
Emergency surgery	20 (54.1)	29 (28.2)	χ^2=8.03	3.00 (1.38-6.52)	0.005*
Elective surgery	17 (45.9)	74 (71.8)		Reference	
General anaesthesia	24 (64.9)	47 (45.6)	χ^2=4.05	2.20 (1.01-4.80)	0.044*
Other types of anaesthesia	13 (35.1)	56 (54.4)		Reference	
Surgery lasting >2 hours	23 (62.2)	39 (37.9)	χ^2=6.51	2.70 (1.24-5.85)	0.011*
Surgery lasting ≤2 hours	14 (37.8)	64 (62.1)		Reference	
Exposure to ≥6 perioperative drugs	29 (78.4)	42 (40.8)	χ^2=15.40	5.27 (2.19-12.64)	<0.001*
Exposure to <6 drugs	8 (21.6)	61 (59.2)		Reference	
Perioperative antibiotic exposure	34 (91.9)	77 (74.8)	χ^2=4.89	3.83 (1.09-13.47)	0.027*
No perioperative antibiotic exposure	3 (8.1)	26 (25.2)		Reference	
Opioid exposure	28 (75.7)	58 (56.3)	χ^2=4.31	2.41 (1.04-5.60)	0.038*
No opioid exposure	9 (24.3)	45 (43.7)		Reference	
Mean number of perioperative drugs	7.8 (2.2)	5.9 (1.8)	t=5.18	MD=1.90 (1.17-2.63)	<0.001*
Mean duration of surgery, minutes	139.7 (46.3)	111.0 (39.1)	t=3.65	MD=28.70 (13.14-44.26)	<0.001*
Mean hospital stay, days	7.2 (3.1)	5.3 (2.3)	t=3.93	MD=1.90 (0.94-2.86)	<0.001*

*Statistically significant at **p<0.05**.

ADR: adverse drug reaction; CI: confidence interval; MD: mean difference.

Table 4 demonstrates the association of patient characteristics and perioperative drug exposure with the occurrence of ADRs. Patients aged 60 years or above had significantly higher odds of developing an ADR than younger patients, with 18 (48.6%) ADR cases being elderly compared with 24 (23.3%) patients in the non-ADR group (OR=3.12, 95% CI: 1.42-6.87; p=0.004). Female

patients were also significantly more likely to experience an ADR than males, with an odds ratio of 2.85 (95% CI: 1.32-6.17; p=0.007). Comorbid illnesses were present in 25 (67.6%) patients with ADRs compared with 38 (36.9%) patients without ADRs, indicating a significantly increased risk among patients with comorbidities (OR=3.56, 95% CI: 1.61-7.90; p=0.001). A previous history of drug allergy was one of the strongest patient-related risk factors, with affected patients having 5.20 times greater odds of developing an ADR (95% CI: 1.70-15.85; p=0.002).

Emergency surgery was significantly associated with ADR occurrence, as 20 (54.1%) patients in the ADR group underwent emergency procedures compared with 29 (28.2%) in the non-ADR group (OR=3.00, 95% CI: 1.38-6.52; p=0.005). General anaesthesia was administered to 24 (64.9%) patients who developed ADRs and 47 (45.6%) patients without ADRs, and it was associated with approximately twofold higher odds of an ADR (OR=2.20, 95% CI: 1.01-4.80; p=0.044). Surgery lasting more than two hours was also significantly associated with ADR occurrence (OR=2.70, 95% CI: 1.24-5.85; p=0.011).

Exposure to six or more perioperative medications showed the strongest medication-related association. It was observed in 29 (78.4%) patients with ADRs compared with 42 (40.8%) patients without ADRs, corresponding to an odds ratio of 5.27 (95% CI: 2.19-12.64; p<0.001). Perioperative antibiotic exposure was associated with 3.83 times higher odds of developing an ADR (95% CI: 1.09-13.47; p=0.027), while opioid exposure was associated with 2.41 times higher odds (95% CI: 1.04-5.60; p=0.038). Patients who developed ADRs received a significantly greater mean number of perioperative drugs than those without ADRs, 7.8 ± 2.2 versus 5.9 ± 1.8, with a mean difference of 1.90 drugs (95% CI: 1.17-2.63; p<0.001). The mean duration of surgery was also significantly longer among patients with ADRs, 139.7 ± 46.3 minutes compared with 111.0 ± 39.1 minutes, with a mean difference of 28.70 minutes (95% CI: 13.14-44.26; p<0.001). Similarly, patients who experienced ADRs had a longer mean hospital stay than those without ADRs, 7.2 ± 3.1 days versus 5.3 ± 2.3 days, with a mean difference of 1.90 days (95% CI: 0.94-2.86; p<0.001). Overall, advanced age, female sex, comorbidity, previous drug allergy, emergency surgery, general anaesthesia, prolonged surgery, polypharmacy, and exposure to antibiotics or opioids were significantly associated with ADR occurrence.

DISCUSSION

Demographic, clinical and perioperative characteristics

The present cross-sectional study evaluated adverse drug reactions associated with perioperative medications among 140 surgical patients. The mean age of the participants was 46.8 ± 14.1 years, and the largest proportion belonged to the 18–39-year age group. Males constituted 59.3% of the study population, producing a male-to-female ratio of approximately 1.46:1. A similar demographic distribution was reported by Patel et al. (2018)[1], who found that most ADRs in a tertiary care emergency department occurred among patients aged 40–60 years and reported a slight male predominance, with a male-to-female ratio of 1.10:1. The relatively younger age profile in the present study may be related to the inclusion of patients undergoing a broad range of elective and emergency surgical procedures rather than only medically ill or elderly hospitalized patients.

The mean body mass index was 24.9 ± 3.8 kg/m², indicating that the average participant was near the upper limit of the normal BMI category. Comorbid illnesses were present in 45.0% of patients, while 10.7% had a previous history of drug allergy. The presence of comorbidities and previous allergy is clinically important because these patients often require additional medications and may have altered drug distribution, metabolism or elimination. Pazan et al. (2021)[2] observed that older adults with multiple chronic illnesses frequently experience polypharmacy and are

consequently more susceptible to drug–drug interactions and medication-related adverse outcomes. Similarly, Masnoon et al. (2017)[3] found that the most commonly accepted definition of polypharmacy was the concurrent use of five or more medications and emphasized its association with an increased risk of ADRs and hospitalization.

Elective procedures accounted for 65.0% of surgeries, whereas 35.0% were emergency operations. General anaesthesia was used in 50.7% of patients, spinal anaesthesia in 30.7%, regional or combined anaesthesia in 12.1%, and local anaesthesia with sedation in 6.4%. The predominance of general anaesthesia increased the number and variety of drugs administered during a relatively short period, including induction agents, opioids, neuromuscular blocking agents, antibiotics, antiemetics and reversal agents. Di Leo et al. (2018)[4] noted that the simultaneous administration of several medications during anaesthesia makes identification of the responsible agent difficult and reported neuromuscular blocking agents, antibiotics, induction agents and opioids among the principal causes of perioperative hypersensitivity reactions.

The mean duration of surgery was 118.6 ± 42.7 minutes, and 44.3% of operations lasted more than two hours. Patients received an average of 6.4 ± 2.1 perioperative drugs, and 50.7% were exposed to six or more medications. These findings demonstrate a substantial perioperative medication burden. Memtsoudis et al. (2020)[5], in a large observational study of more than 1.5 million joint replacement procedures, highlighted that perioperative outcomes were influenced by the number and combination of care components and medications used. Although the study focused on enhanced recovery practices, it supports the importance of systematically reviewing the entire perioperative treatment package rather than evaluating a single drug in isolation.

The mean postoperative hospital stay was 5.8 ± 2.7 days. ADRs occurred in 37 of the 140 patients, giving an incidence of 26.4%. This incidence was higher than the assumed reference proportion of 20%, although the difference narrowly missed statistical significance. The observed incidence was higher than that reported in several hospital-wide pharmacovigilance studies, probably because the present investigation used active perioperative monitoring and included expected reactions such as nausea, vomiting, hypotension, excessive sedation and allergic manifestations. Passive reporting systems frequently underestimate ADR occurrence because mild or transient reactions may not be documented.

Incidence and pattern of adverse drug reactions

Among the 37 patients with ADRs, 83.8% experienced one reaction and 16.2% experienced more than one. Gastrointestinal reactions were the most common organ-system category, accounting for 32.4%, followed by cutaneous or allergic reactions in 21.6%, cardiovascular reactions in 18.9%, central nervous system reactions in 10.8%, and respiratory reactions in 8.1%. Nausea and vomiting were the most frequently observed clinical manifestations, affecting 29.7% of ADR cases. Gan et al. (2020)[6], in the Fourth Consensus Guidelines for postoperative nausea and vomiting, recognized nausea and vomiting as among the most frequent complications following anaesthesia and surgery. The guidelines identified patient characteristics, anaesthetic techniques and postoperative opioid exposure as major contributing factors. The prominence of gastrointestinal ADRs in the present study is therefore consistent with established perioperative evidence.

Stoops and Kovac (2020)[7] similarly emphasized that postoperative nausea and vomiting remain important causes of patient discomfort, delayed recovery and dissatisfaction and are strongly influenced by opioid use and anaesthetic exposure. In the present study, opioid analgesics were the second most frequently suspected drug class and were implicated in 24.3% of reactions. Opioid-related nausea, vomiting, sedation and respiratory depression may therefore explain a considerable proportion of the gastrointestinal, neurological and respiratory manifestations observed.

Antibiotics were the most commonly suspected drug class, accounting for 29.7% of ADRs. This finding agrees with Patel et al. (2018)[1], who reported that anti-infective drugs were the most frequently implicated class, accounting for 30.13% of ADRs in a tertiary care emergency medicine department. Their study also found cardiovascular drugs to be the next most common group. The similarity in the proportion attributable to antibiotics suggests that antimicrobial exposure remains an important source of hospital ADRs, particularly where prophylactic antibiotics are routinely administered before surgical incision.

The predominance of antibiotics as suspected agents is also supported by Harper et al. (2018)[8], who reported findings from the Sixth National Audit Project of the Royal College of Anaesthetists. Antibiotics accounted for 94 of 199 identified culprit agents in life-threatening perioperative anaphylaxis, followed by neuromuscular blocking agents in 65 cases. The authors estimated an incidence of approximately one perioperative anaphylactic event per 10,000 anaesthetics. Although the present study assessed all levels of ADR severity rather than only anaphylaxis, the findings similarly identify antibiotics as an important perioperative risk group.

Dewachter and Savic (2019)[9] also reported that antibiotics and neuromuscular blocking agents were the leading triggers of IgE-mediated perioperative anaphylaxis. Based on NAP6 findings, antibiotics accounted for approximately 48% and neuromuscular blocking agents for 25% of identified causative agents. In comparison, neuromuscular blocking agents accounted for only 8.1% of ADRs in the present study. This lower proportion is understandable because most reactions in the present study were non-serious and included common dose-related events, whereas perioperative anaphylaxis studies selectively examine severe hypersensitivity reactions.

The timing of ADR onset was equally divided between the intraoperative period and the first 24 postoperative hours, with each accounting for 37.8% of reactions. The remaining 24.3% occurred more than 24 hours after surgery. This temporal pattern reflects the immediate exposure to anaesthetic agents, antibiotics, opioids and neuromuscular blockers during surgery, followed by continuing exposure to analgesics, antibiotics and antiemetics during early recovery. Admass et al. (2023)[10], in a systematic review of perioperative anaphylaxis management, noted that severe reactions commonly occurred shortly after induction because most causative agents were administered intravenously during this period. While the present study included both hypersensitivity and non-hypersensitivity ADRs, its substantial proportion of intraoperative reactions supports the need for continuous monitoring immediately after medication administration.

Withdrawal of the suspected drug was required in 35.1% of ADR cases, symptomatic treatment was given in 32.4%, and dose reduction or drug substitution was undertaken in 21.6%. Observation alone was sufficient in 10.8%. Most reactions were non-serious, accounting for 83.8%, while only 16.2% were serious. Complete recovery was documented in 83.8% of affected patients, with 10.8% recovering at discharge and 5.4% experiencing prolonged hospitalization. In contrast, Patel et al. (2018)[1] reported that 52.4% of ADRs presenting to an emergency department were serious, with 44.1% completely recovered and 43.2% recovering. The lower seriousness and higher complete-recovery rates in the present study may be attributed to prospective detection of mild perioperative symptoms before they progressed and the availability of immediate monitoring and intervention in the operating room and recovery unit.

Causality, severity and preventability

According to the WHO–UMC causality assessment, 51.4% of ADRs were categorized as probable or likely, 35.1% as possible, 8.1% as certain and 5.4% as unlikely. The Naranjo scale produced comparable findings, with 54.1% classified as probable, 37.8% as possible and 8.1% as definite.

The mean Naranjo score was 5.7 ± 1.8, which corresponded predominantly to the probable category. Patel et al. (2018)[1] similarly reported that 57.64% of ADRs were probable or likely according to standardized causality assessment. The close agreement between their result and the present study supports the consistency of WHO–UMC and Naranjo assessments in hospital pharmacovigilance.

In comparison, Kassere et al. (2019)[11] found that approximately 80% of anticoagulant-associated ADRs were categorized as possible using the WHO and Naranjo scales. Differences in causality distribution may result from the nature of the drugs studied, the presence of multiple concomitant medications, limited rechallenge information and difficulty excluding alternative clinical causes. In perioperative practice, numerous drugs are administered in rapid succession, and this can make definite attribution difficult.

The Modified Hartwig and Siegel severity scale classified 48.6% of reactions as moderate, 43.2% as mild and 8.1% as severe. Level 3 reactions were the most common individual severity level. Patel et al. (2018)[1] reported a considerably higher proportion of severe ADRs at 18.78%, which may reflect the emergency-department setting and inclusion of ADRs responsible for hospital admission. Conversely, Kassere et al. (2019)[11] found that 97.56% of anticoagulant-related reactions were mild and only 2.44% were severe. The present findings therefore lie between these two studies, indicating that perioperative ADRs were commonly mild to moderate but that a small clinically important proportion required substantial intervention.

Using the Modified Schumock and Thornton criteria, 18.9% of reactions were definitely preventable, 48.6% were probably preventable and 32.4% were not preventable. Thus, 67.6% of all ADRs were considered definitely or probably preventable. Kassere et al. (2019)[11] reported an even higher preventability rate, with 97.56% of anticoagulant-associated ADRs categorized as probably preventable. In contrast, Patel et al. (2018)[1] found that 64.19% of reactions were not preventable and 17.03% were definitely preventable. These differences may be explained by variations in the clinical departments, drugs evaluated, monitoring systems and interpretation of preventability criteria. The high preventable proportion in the present study suggests opportunities for better allergy documentation, individualized dose selection, avoidance of unnecessary polypharmacy, appropriate antiemetic prophylaxis and closer haemodynamic and respiratory monitoring.

Factors associated with ADR occurrence

Patients aged 60 years or above had 3.12 times higher odds of developing ADRs than younger patients. Age-related reductions in renal and hepatic function, altered drug distribution, increased pharmacodynamic sensitivity and greater comorbidity burden may contribute to this association. Pazan et al. (2021)[2] highlighted that older adults have high levels of multimorbidity and medication exposure and consequently face increased risks of drug interactions, hospitalization and other adverse clinical outcomes. The finding supports careful medication reconciliation and dose adjustment in elderly surgical patients.

Female patients had 2.85 times higher odds of ADRs than males. This association may be partly explained by the higher susceptibility of women to postoperative nausea and vomiting and differences in body composition, hormonal influences and pharmacokinetics. Gan et al. (2020)[6] identified female sex as a major independent predictor of postoperative nausea and vomiting. Since nausea and vomiting were the leading ADR manifestations in the present study, this established sex-related predisposition may have contributed substantially to the observed association.

Comorbid illnesses were associated with 3.56 times higher odds of ADRs. Patients with comorbidities frequently require chronic medicines in addition to perioperative drugs, increasing

the possibility of drug–drug and drug–disease interactions. A previous history of drug allergy was associated with 5.20 times higher odds of an ADR, representing one of the strongest patient-related associations. This finding emphasizes the importance of documenting the exact suspected drug, reaction type, severity and timing during preoperative assessment rather than recording an unspecified "drug allergy." Di Leo et al. (2018)[4] and Dewachter and Savic (2019)[9] stressed that identification of previous hypersensitivity and the likely culprit agent is essential to prevent repeated perioperative exposure.

Emergency surgery increased the odds of ADR occurrence threefold. Emergency procedures often allow less time for medication reconciliation, optimization of comorbidities, review of previous allergic reactions and correction of physiological abnormalities. General anaesthesia was associated with 2.20 times higher odds of ADRs than other anaesthetic techniques. This association may not be attributable to general anaesthesia alone; rather, it may reflect the greater number of medications, airway interventions and physiological disturbances associated with such procedures. Burgess et al. (2021)[12] reported that anaesthesia-related adverse events were influenced by patient status, urgency and the complexity of perioperative care, supporting increased vigilance during higher-risk procedures.

Surgery lasting longer than two hours was associated with 2.70 times higher odds of ADRs. Patients with ADRs also had a significantly longer mean surgical duration than those without ADRs, with a difference of 28.7 minutes. Longer operations generally require repeated dosing of anaesthetics, opioids, muscle relaxants and vasoactive drugs and expose patients to prolonged physiological stress. However, because the present study was cross-sectional, prolonged surgery may function both as a risk marker and as an indicator of operative complexity; causality cannot be established.

Exposure to six or more perioperative drugs was the strongest medication-related factor, increasing the odds of ADR occurrence 5.27 times. Patients who developed ADRs received an average of 7.8 medications compared with 5.9 among those without ADRs. This result is consistent with Masnoon et al. (2017)[3], who identified five or more drugs as the most common operational definition of polypharmacy, and with Pazan et al. (2021)[2], who described increasing medication count as an important determinant of adverse drug events. Every additional medication may introduce an independent risk of toxicity and may also interact with other drugs, making the association biologically plausible.

Perioperative antibiotic exposure was associated with 3.83 times higher odds of an ADR. This agrees with the finding that antibiotics were the most commonly suspected drug class and with the observations of Harper et al. (2018)[8], Patel et al. (2018)[1], and Dewachter and Savic (2019)[9]. Nevertheless, the wide confidence interval indicates limited precision because most patients received prophylactic antibiotics, leaving relatively few unexposed patients for comparison.

Opioid exposure increased the odds of ADR occurrence 2.41 times. Opioids are associated with nausea, vomiting, sedation, pruritus, urinary retention and respiratory depression, several of which were observed in the present study. Gan et al. (2020)[6] and Stoops and Kovac (2020)[7] described perioperative opioid use as an important modifiable contributor to nausea and vomiting and supported opioid-sparing multimodal analgesic strategies in at-risk patients.

Patients with ADRs had a mean hospital stay 1.9 days longer than those without ADRs. ADR-related observation, supportive treatment, substitution of medications and management of complications may delay postoperative recovery and discharge. However, longer admission could also increase the period during which ADRs were detected. The association should therefore be

interpreted as a relationship rather than proof that every additional hospital day was directly caused by the ADR.

CONCLUSION

The present study demonstrated that adverse drug reactions associated with perioperative medications occurred in a substantial proportion of surgical patients, with an overall incidence of 26.4%. Gastrointestinal reactions, particularly nausea and vomiting, were the most frequently observed manifestations, followed by cutaneous or allergic and cardiovascular reactions. Antibiotics, opioid analgesics and general anaesthetic agents were the most commonly suspected drug classes. Most ADRs were single, non-serious and resulted in complete recovery; however, a small proportion caused serious reactions or prolonged hospitalization.

Causality assessment using the WHO–UMC and Naranjo scales showed that most reactions were probable or possible, while severity assessment indicated that the majority were mild to moderate. Importantly, more than two-thirds of the ADRs were considered definitely or probably preventable. Advanced age, female sex, comorbid illness, previous drug allergy, emergency surgery, general anaesthesia, prolonged surgery, exposure to six or more perioperative medications, and use of antibiotics or opioids were significantly associated with ADR occurrence. Patients who developed ADRs also had longer surgical duration and postoperative hospital stay. These findings emphasize the need for careful preoperative assessment, accurate allergy documentation, rational perioperative prescribing, avoidance of unnecessary polypharmacy, appropriate antiemetic and analgesic strategies, and active pharmacovigilance throughout the perioperative period.

LIMITATIONS OF THE STUDY

The study had certain limitations. First, it was conducted at a single tertiary care hospital, which may limit the generalizability of the findings to other healthcare settings. Second, the cross-sectional observational design allowed identification of associations but could not establish a definite cause-and-effect relationship between risk factors and ADR occurrence. Third, the relatively small sample size and limited number of ADR cases reduced the precision of some estimates, particularly for serious and uncommon reactions.

The study included patients from different surgical specialties and anaesthetic techniques, resulting in heterogeneity in drug exposure and operative risk. Some mild or transient reactions may have been missed if they were not reported by patients or documented in clinical records. Causality assessment was also challenging because several medications were administered within a short period, making identification of a single responsible drug difficult. Rechallenge was generally not ethically or clinically feasible, limiting the number of reactions categorized as definite or certain. Laboratory confirmation and allergy testing were not performed in all suspected cases. In addition, patients were followed only until hospital discharge; therefore, delayed ADRs occurring after discharge may not have been captured. Residual confounding from disease severity, surgical complexity and concurrent medications may also have influenced the observed associations.

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