Postoperative Delirium in Indian Patients Following Major Abdominal Surgery for Cancer: Risk Factors and Associations

Vibhawari Dhakharia^{1,2} • Subir Sinha³ • Jaydip Bhaumik⁴

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Abstract Postoperative delirium (POD) is not uncommon following major abdominal surgery with its incidence ranging between five and 51%. As cancer affects disproportionately, the population older than 65 years and as delirium is more common in the elderly, surgical oncology patients are at a higher risk of developing POD. The present study was undertaken to explore the impact and associations of POD in Indian patients undergoing oncological major abdominal surgery. A retrospective review of the electronic medical records in a tertiary cancer care institution of all postoperative patients who had undergone major gastrointestinal gynaecological and urological abdominal surgery for cancer and required psycho-oncology referral was performed. Patient, surgery and postoperative outcome-related data were collected. Statistical analysis was performed using univariate and multivariate logistic regression analysis. Out of 824 patients who underwent major abdominal surgery, 33 patients (4.0%) were diagnosed with POD. In univariate analysis, older age and history of addiction were found to be statistically significantly associated with POD ($p < 0.001$). Among the postoperative factors, respiratory complications ($p < 0.001$), sepsis ($p < 0.05$), ICU stay > 24 h ($p < 0.05$) and electrolyte impairment ($p < 0.05$) were the significant associations with the POD.

Thirty-day mortality was higher in the POD group ($p < 0.05$). In multivariate logistic regression analysis, advanced age, addictions, respiratory complications and sepsis were found to be significant associations with POD, $p < 0.001$. Postoperative delirium is associated with higher mortality. Older age, postoperative respiratory complications and sepsis are common contributory factors of postoperative delirium.

Keywords Postoperative delirium · Major abdominal surgery · Cancer · Surgical oncology

Introduction

The brain is vulnerable during the perioperative period among patients of all ages. Neurobehavioral disturbances are among the commonly seen postoperative complications, of which three distinct forms are identified: emergence delirium, postoperative cognitive decline and the most severe form—postoperative delirium (POD) [1]. *ICD-10 Chapter V Mental and Behavioural Disorders* defines delirium as an etiologically nonspecific organic cerebral syndrome characterised by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep-wake schedule. The duration is variable and the degree of severity ranges from mild to very severe with POD classified as a separate entity [2]. Delirium could be subclassified into hypoactive and hyperactive subtypes and can be diagnosed based on clinical features [3]. Several screening instruments are available to aid the clinical assessment of delirium. As per the American College of Critical Care Medicine, the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most valid and reliable delirium screening tools [4].

✉ Vibhawari Dhakharia
vibhawari9dr@gmail.com

¹ Department of Gynaecological Oncology, Health Care Global Enterprises Ltd (HCG), Bangalore, India

² # 121, BEML Layout, 3rd Main Road, ITPL Road, Near Kundalahalli Gate, Bangalore 560066, India

³ Department of Statistics, Tata Medical Center, Kolkata, India

⁴ Department of Gynaecological Oncology, Tata Medical Center, Kolkata, India

POD is a form of delirium that manifests in patients who have undergone surgical procedures and anaesthesia. The incidence peaks between 1 and 3 days after the operation. It must be differentiated from emergence delirium which is characterised by agitation, restlessness and hyperactivity, and occurs in 8–20% of patients after awakening from general anaesthesia, especially in younger people; however, it does not fluctuate and lasts only for a short period of time [5, 6].

Management of many cancers, mainly gastrointestinal, hepatobiliary, gynaecological and urological cancers, involve radical abdominal surgeries. Radical cancer surgeries are complex, extensive and prolonged and result in significant morbidity and mortality when attempted for cure [7]. POD is not uncommon following major abdominal surgery with its incidence ranging between five and 51% [8]. As cancer affects disproportionately to population older than 65 years [9] and as delirium is more common in elderly, surgical oncology patients are at a higher risk of developing POD.

The predisposing factors for the development of the POD in surgical oncology have been previously described by various prospective observational and retrospective studies. The present study was undertaken to explore the impact and associations of POD in Indian patients undergoing major abdominal surgery for the treatment of cancer.

Methods

The present study was conducted in a tertiary comprehensive cancer care centre where a multidisciplinary team including the surgical team, anaesthetic team, intensivists and a liaison psycho-oncology service were involved in the routine postoperative management of the surgical oncology patients. Patients at the earliest clinical suspicion of symptoms related to development of delirium were referred to the liaison psychiatrist and simultaneously investigated by the surgical team and medical team so as to identify the cause of delirium. The referral to the psycho-oncology service which consisted of a consultant psychiatrist and a psychologist was to confirm the diagnosis and to manage the agitation in hyperactive delirium and other behavioural symptoms of delirium. Delirium was diagnosed by the consultant psychiatrist based on WHO ICD 10 criteria. There were other surgical oncology patients who underwent major abdominal surgery and required postoperative referral to the liaison psychiatrist for other psychiatric symptoms. The group of patients who were diagnosed to have delirium and seen by psycho-oncology services were compared with this other group of patients who were also seen by the psycho-oncology services and were diagnosed to have a condition other than delirium.

We undertook a retrospective review of the electronic medical record (EMR) of all postoperative surgical oncology patients who had undergone major gastrointestinal, gynaecological and urological abdominal surgery between

November 2011 and November 2013 and required psycho-oncology referral during postoperative hospitalisation. Patient-related, surgery-related and postoperative outcome-related data were collected.

Patient characteristics studied were age, sex, comorbidities, addiction (diagnosis based on history taken and information disclosed at first visit to the outpatient department), pre-existing psychiatric illness, preoperative body mass index (BMI), serum albumin level, neo-adjuvant treatment (chemotherapy and/or radiotherapy), chronic use of narcotic analgesics, primary organ of cancer, stage of disease, intent of treatment, performance status and American Society of Anaesthesiologists (ASA) fitness to surgery grade. The intraoperative factors investigated were type of anaesthesia, surgery performed, extent of surgery, duration of surgery and intraoperative blood loss. Postoperative factors investigated were length of ICU stay, blood transfusion, electrolyte and metabolic derangement, hyponatremia, sepsis other than respiratory (diagnosis based on clinical assessment supported by investigation findings including cultures, acute phase reactants and imaging), respiratory complications (including respiratory infections, prolonged intubation and respiratory support) and serum albumin level. The outcome measures studied were duration of postoperative hospital stay and mortality within 30 days. In the delirium group, postoperative day of onset of delirium and duration of delirium were noted.

Both univariate and multivariate analysis were performed. Student's *t* test was used to compare the continuous variables while chi-square test was used to compare the binary variables and logistic regression was used for multivariate analysis. For numerical continuous and discrete variables, mean with range was used while for the categorical binary or ordered variables, frequency (percentage) was used. The statistical significance was set at $p < 0.05$.

Results

During the period of Nov. 2011 to Nov. 2013, 824 patients underwent major abdominal cancer surgery at the institution. Out of these, 81 (9.8%) patients required postoperative psycho-oncology referral. Thirty-three patients (4.0%) were diagnosed with POD (group 1). These patients were compared with the 48 patients who were not diagnosed with delirium (group 2).

In 26 (78.8%) out of the 33 patients with POD, the onset of delirium was within first postoperative week and delirium lasted for an average of 1 week (7.4 days). Distribution of the population in relation to the primary organ of cancer is given in Table 1. POD was most frequently diagnosed in those who had undergone gastrointestinal (GI) and hepatobiliary surgeries (20.1% of total referred patients). Details of surgeries performed are given in Table 2.

Table 1 Primary organ of cancer in the study population

Primary organ of cancer	POD <i>n</i> = 33 (%)	No POD <i>n</i> = 48 (%)
Gastrointestinal total	14 (42.4)	13 (27.1)
Oesophagus	2	1
GE junction	1	2
Stomach	2	1
GIST	0	2
Duodenal	1	0
Periampullary	1	2
Appendix	1	0
Colorectal	6	5
Hepatobiliary total	3 (9.1)	4 (8.3)
HCC	1	1
Gall bladder	1	1
Pancreas	1	1
Distal CBD	0	1
Gynaecological total	10 (30.3)	27 (56.2)
Ovary/PPCA/Tubal	5	20
Endometrium	4	6
Cervix	0	1
Vulva	1	0
Urological total	5 (15.6)	3 (6.3)
Bladder	1	3
Kidney	4	0
Others total	1 (3.03)	1 (2.1)

Univariate Analysis The patients who were diagnosed with POD were significantly older (mean age 64.5 years) compared to the patients who were not (mean age of 52.2 years, $p < 0.001$). POD was found to be equally prevalent in both genders ($p = 0.61$). History of addiction was significantly associated with the POD ($p < 0.001$). There was no difference between the two groups in other patient characteristics studied. None of the intraoperative factors analysed were found to be significantly associated with the occurrence of POD. Among the postoperative factors, association of POD and respiratory complications was found to be statistically significant ($p < 0.001$). Other significant associations were ICU stay more than 24 h, electrolyte/metabolic impairment and sepsis/infections other than respiratory, ($p < 0.05$, Table 3). Patients in the POD group were found to have a poorer surgical outcome with a significantly higher 30-day mortality ($p = 0.02$). However, the postoperative hospital stay was found to be similar in both the groups ($p = 0.05$, Table 3).

Multivariate Analysis Advanced age, addictions, respiratory complications and sepsis were associated with postoperative delirium, and the associations were statistically significant ($p < 0.001$, Table 4).

Table 2 Surgeries performed

Surgeries performed	POD <i>n</i> = 33 (%)	No POD <i>n</i> = 48 (%)
Gastrointestinal		
Oesophagectomy	3 (9.09)	2 (4.16)
Cytoreductive	2 (6.06)	
LAR	3 (9.09)	3 (6.25)
Ileocecal resection	1 (3.03)	2 (4.16)
Gastrectomy	2 (6.06)	2 (4.16)
Sigmoid colectomy	2 (6.06)	2 (4.16)
Posterior exenteration		1 (2.08)
Sugarbaker procedure	2 (6.06)	1 (2.08)
Hepatobiliary-pancreatic		
Radical cholecystectomy	1 (3.03)	1 (2.08)
Extended hepatectomy	1 (3.03)	
Whipple's procedure	2 (6.06)	3 (6.25)
Gynaecological		
IDS	4 (12.12)	6 (12.5)
Staging for endometrial Ca	2 (6.06)	14 (29.16)
Anterior exenteration	2 (6.06)	
Urological		
Nephrectomy	2 (6.06)	
Radical cystectomy	2 (6.06)	3 (6.25)
Others	2 (6.06)	8 (16.66)

Discussion

POD is a known complication following major abdominal surgeries especially in the elderly and has been widely studied worldwide. However, very little work has been done in this field in India with most of the studies done on delirium in medical settings and general practice [10]. There are a few published studies from India on POD [11] but none has been reported on patients undergoing cancer surgery. To the best of our knowledge, this is the first ever study reporting POD in Indian surgical oncology patients following major abdominal surgery.

In our study, 33 patients (4%) of the total 824 patients undergoing major abdominal cancer surgeries were diagnosed with POD during the study period which is less than the average reported incidence. As it was not possible to screen all 824 patients who underwent major oncological abdominal surgeries during the study period, for the presence or absence of POD in a low-resource setting, only those patients who were referred to psycho-oncology services due to pre-existing mental health issues or due to the development of any psychiatric symptoms during postoperative period and thus in turn screened ($n = 81$) were included in the study. It is possible that there could be a few more patients that would have been diagnosed with POD had there been a screening system in place.

Table 3 Univariate analysis: significant associations of perioperative factors with postoperative delirium

Perioperative factors	POD <i>n</i> = 33	No POD <i>n</i> = 48	<i>P</i> value
Patient characteristics			
Mean age (range)	64.5 (41–80)	52.2 (17–78)	
< 60 years	6 (18.2%)	31 (64.5%)	< 0.001
≥ 60 years	27 (81.8%)	17 (35.5%)	
Addiction			
Nil	24 (72.7%)	43 (89.5%)	< 0.001
Alcohol	3 (9.1%)	1 (2.1%)	
Tobacco	6 (18.2%)	4 (8.3)	
Comorbidities			
None	8 (24.2%)	23 (47.9)	0.05
One	9 (27.3%)	13 (27.1)	
Two or more	16 (48.5%)	12 (25%)	
Postoperative factors			
ICU stay			
24 h	7 (21.2%)	24 (50%)	0.01
> 24 h	26 (78.8%)	24 (50%)	
Electrolyte and metabolic impairment			
Yes	17 (51.5%)	13 (27.1%)	0.02
No	16 (48.5%)	35 (72.9)	
Infection other than respiratory			
Yes	20 (60.6%)	16 (33.3%)	0.01
No	13 (39.4%)	32 (66.7%)	
Respiratory complications			
Yes	15 (45.5%)	3 (6.3%)	<0.001
No	18 (54.5%)	45 (93.8%)	
Surgical outcome-related factors			
Duration of post op hospital stay			
Up to 7 days	5 (15.2%)	9 (18.8%)	0.05
7–14 days	8 (24.2%)	21 (43.8%)	
> 14 days	18 (54.5%)	16 (33.3%)	
Mortality within 30 days			
Yes	5 (15.2%)	1 (2.1%)	0.02
No	28 (84.8%)	47 (97.9%)	

POD is more commonly seen in older surgical patients. The older the patient, the higher the chances of associated age-related cognitive decline, frailty and medical comorbidities. All of these increase the risk of POD with increasing age. This association with older age has been proven in many stud-

Table 4 Multivariate logistic model: significant associations of perioperative factors with postoperative delirium

Variables	Odds ratio	<i>P</i> value
Age in years	4.17	< 0.001
Addictions	3408	< 0.001
Respiratory complications	86.45	< 0.001
Sepsis	2.22	< 0.001

ies [8]. The present study is in agreement with the results of the previous studies. The history of addiction was also found to be significantly associated with the development of POD ($p < 0.001$). Two large and many smaller studies have shown significant association between alcohol abuse and increased risk of POD [12, 13].

Although male sex has been associated with increased risk for development of POD in many studies including few large prospective studies [14], our study showed it to be equally prevalent in both the genders. Preoperative multiple comorbid status has been one of the most commonly reported risk factor for the development of POD [15]. No association was found in the present analysis. Pre-existing depressive and anxiety disorders, which are common in cancer patients, have been reported in few studies to increase the incidence of postoperative confusion [16, 17]. In the present analysis, none of the patients with known pre-existing psychiatric illness developed POD. As these patients were under supervision of the psychiatric team and under different psychotropic medications, it is possible that POD did not manifest in these patients. Moreover, as not all the patients were subjected to preoperative psychiatric assessment, possibility of undiagnosed underlying psychiatric illness in those with delirium could not be ruled out.

Advanced stage of disease usually adds to the morbidity in surgical oncology patients; however, in our study, we did not find any association between stage of disease and POD as delirium was seen equally frequent in early and advanced stage disease ($p = 0.66$).

Other preoperative factors studied were preoperative ECOG performance status, ASA grade, preoperative BMI and preoperative serum albumin, which are important considerations during the preoperative assessment of the patients' functional and nutritional status. Preoperative functional status especially in elderly patients has been reported to be associated with the occurrence of POD. Low preoperative serum albumin which is a marker for poor preoperative nutritional status has been reported as an independent risk factor for POD in patient undergoing colorectal surgery [18]. These were not found to be associated with the development of POD in the present analysis.

None of the intraoperative factors analysed in the present study were found to have a statistically significant association with the development of POD. Similar results were seen in a retrospective study by Fanning et al. in gynaecologic oncology patients [19].

Among the postoperative factors studied, in multivariate analysis, statistically significant associations were found with respiratory complications and sepsis with the development of POD ($p < 0.001$). Other significant associations found were ICU stay more than 24 h ($p < 0.01$) and electrolyte imbalance ($p < 0.01$). Mortality within 30 days was found to be significantly associated with the POD ($p = 0.02$). Although we did not find significant association with the longer duration of

hospital stay ($p = 0.05$), as found in other studies, it might be due to the small sample of population studied.

Five patient died in the delirium group ($n = 33$) within 30 days of surgery; however, only one patient died in the non-delirium group ($n = 48$) [$p = 0.02$]. Out of the five patients who died in the delirium group, one was treated for advanced renal cell carcinoma, two had Ca lower one third oesophagus, one had Ca endometrium and one had adenocarcinoma GE junction. All the patients were managed postoperatively by a multidisciplinary team including the surgical team, anaesthetic team, intensivist and the liaison psycho-oncology service. The primary analysis consisted of thorough clinical assessment, blood investigations including acute phase reactants, urinalysis, culture and sensitivities as and when indicated, and imaging (ultrasound, X-ray and CT scan).

Ganai et al. in a retrospective case series of 89 geriatric patients who underwent major abdominal surgery concluded that adverse outcomes (postoperative delirium and mortality) correlated only with hyperglycaemia, poor nutritional and functional status [20]. In our study, delirium group and non-delirium groups were similar in the above-mentioned variables. Robinson et al. in a prospective study of 144 patients who underwent major abdominal (40%), thoracic (53%) and vascular (7%) surgeries found pre-existing cognitive dysfunction as the strongest predictor of development of postoperative delirium. They also found outcomes including 6-month mortality were worse in patients who developed postoperative delirium [15]. In our study, we did not check the patients for pre-existing cognitive dysfunction preoperatively which is one of its limitations; however, our study agreed with high 30-day mortality in patients with POD ($p = 0.02$). The mortality was higher probably because factors that led to the mortality contributed to the development of POD too.

The development of postoperative delirium is associated with higher mortality which makes its management an essential part of postoperative care especially in the elderly. Although discussion on the pharmacological management of POD is beyond the scope of this study, a brief mention of the nonpharmacological interventions appears necessary.

There is now growing evidence that nonpharmacological interventions utilising educational and noneducational approaches can help prevent delirium in many patients [21]. Delirium education of the health care professionals should be an essential part of the management of POD. In addition, implementation of multicomponent nonpharmacologic intervention programs delivered by an interdisciplinary team for the prevention of POD in at-risk older adults and to improve outcome in older adults with POD should be considered by the health care professionals. Some of the nonpharmacological strategies include sensory and mobility enhancement, cognitive orientation and stimulation, sleep enhancement by nonpharmacologic sleep protocols, nutrition and fluid repletion enhancement [22].

Conclusion

The elderly cancer patients undergoing major abdominal surgery are at significantly higher risk of postoperative delirium. Respiratory complications and sepsis are common contributory factors. Postoperative delirium is associated with increased mortality making its early detection and management an important aspect of the postoperative management of surgical oncology patients. Management of postoperative delirium requires a multidisciplinary team approach. Preoperative psychiatric assessment preferably by a consultant psychiatrist, when feasible, should be a part of preoperative optimization of patients with cancer as they are at a high risk of psychological distress. This should include counselling and medications if required. High degree of clinical suspicion for an early diagnosis and prompt treatment is the key in the management of postoperative delirium.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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