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β-adrenergic blockade is associated with a reduced risk of 90-day mortality after surgery for hip fractures

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ABSTRACT

Background There is a significant postoperative mortality risk in patients subjected to surgery for hip fractures. Adrenergic hyperactivity induced by trauma and subsequent surgery is thought to be an important contributor. By downregulating the effect of circulating catecholamines the increased risk of postoperative mortality may be reduced. The aim of the current study is to assess the association between regular β-blocker therapy and postoperative mortality.

Methods This cohort study used the prospectively collected Swedish National Quality Registry for hip fractures to identify all patients over 40 years of age subjected to surgery for hip fractures between 2013 and 2017 in Örebro County, Sweden. Patients with ongoing β-blocker therapy at the time of surgery were allocated to the β-blocker-positive cohort. The primary outcome of interest was 90-day postoperative mortality. Risk factors for 90-day mortality were evaluated using Poisson regression analysis.

Results A total of 2443 patients were included in this cohort of whom 900 (36.8%) had ongoing β-blocker therapy before surgery. The β-blocker positive group was significantly older, less fit for surgery based on their American Society of Anesthesiologists classification and had a higher prevalence of comorbidities. A significant risk reduction in 90-day mortality was detected in patients receiving β-blockers (adjusted incidence rate ratio=0.82, 95% CI 0.68 to 0.98, p=0.03).

Conclusions β-blocker therapy is associated with a significant reduction in 90-day postoperative mortality after hip fracture surgery. Further investigation into this finding is warranted.

Level of evidence Therapeutic study, level III; prognostic study, level II.

BACKGROUND

Hip fractures predominantly affect the elderly. With an ageing global population an increase in the incidence of such events is expected.[1] The majority of hip fractures are treated surgically, as opposed to conservatively, and are associated with high postoperative mortality. The risk of early postoperative mortality ranges from 10% to 16%,[2] and is as high as 27% in the first postsurgical year.[2–4] Despite new improved innovations in orthopedic surgery and multidisciplinary team approaches to decision-making, postoperative mortality numbers after surgery for hip fractures have remained unchanged during the last decade.[2 5]

There is high level of scientific evidence that β-adrenergic blockade in cardiac surgery is associated with better overall outcomes.[6] Recent studies have detected a significant association between β-adrenergic blockage and an increase in survival in patients suffering from severe traumatic injuries,[7–9] and those subjected to major intra-abdominal surgery.[10 11] It is a held hypothesis that such positive outcomes are the results of the β-blockers' (BB) ability to downregulate the hyperadrenergic activity which is generated by the trauma and surgery.[12 13] The adrenergic hyperactivity state imposes great strain on the cardiovascular system, metabolic and hormonal pathways, as well as immunomodulation. This ultimately leads to a decreased recovery potential and an increased risk of adverse postoperative outcomes such as sepsis, cardiovascular adverse events, multiorgan failure, and ultimately death.[14 15]

There are no previous studies investigating the association between β-adrenergic blockade and mortality in patients undergoing orthopedic surgery for hip fractures. The aim of the current retrospective cohort study is to investigate if such a relationship exists with the hypothesis that BB therapy will reduce the risk of short-term postoperative mortality.

METHODS

The study population was obtained from the Rikshöft registry.[16] The Rikshöft registry is a prospectively collected national registry for hip fractures and was set up in 1988. All consecutive patients aged 40 years and above who underwent primary surgery for an isolated hip fracture between January 1, 2013 and December 31, 2017 in Örebro County were included and retrospectively analyzed. Örebro County has three hospitals: Örebro University Hospital and two university-affiliated regional hospitals. Patients with a pathological fracture were excluded. Patients who suffered a hip fracture on both the right and the left hip during the study period were included as two separate cases unless they died within the 90-day postoperative follow-up period. In the event of a patient having a second surgery within the 90-day follow-up period they were only counted as one case, that is, the first hip fracture surgery. Variables obtained from the Rikshöft registry were age, sex, type of fracture, date of hospital admission, American Society of Anesthesiologists (ASA) classification, surgical method and date of hospital discharge. In addition to registry data, patients' electronic medical records

were reviewed to obtain comorbidity data, time of death and information regarding BB prescriptions and administration. Patients were divided into BB positive (+) and BB negative (−) groups based on whether or not they had ongoing BB therapy at the time of surgery. Comorbidity data were used to calculate a Charlson Comorbidity Index (CCI) for each patient.[17] The CCI includes the diagnosis of myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular events, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, liver disease, diabetes mellitus, hemiplegia, chronic kidney disease, cancer, leukemia, lymphoma and AIDS. The review of patients' electronic medical records also allowed the completion of missing data from the national Rikshöft registry.

Statistical analysis

Patient demographics and clinical characteristics were compared between the groups using the χ^2 test for categorical variables and the Student's t-test or Mann-Whitney U test for continuous variables as appropriate. The primary outcome of interest was 90-day mortality after hip fracture surgery. The crude incidence rates of 30-day and 90-day mortality in the two groups were compared using the χ^2 test and hospital length of stay was compared using the Mann-Whitney U test. Poisson regression models with robust standard errors of variance were deployed to evaluate the effect of BB therapy on 30-day and 90-day postoperative mortality. The time from surgery to death or to the end of the 90-day follow-up period was used as an offset in the Poisson regression models. The regression models were adjusted for age, sex, ASA classification, CCI, type of fracture, and surgical intervention. Adjustment for type of fracture and surgical intervention was made to control for the stress reaction caused by the injury itself as well as the surgical trauma. Results are reported as incidence rate ratio (IRR) with 95% CI. Statistically significant results were defined as a p value <0.05 throughout all statistical analyses. No power analysis for sample size was performed. All statistical analyses were preformed using Statistical Package for Social Science (SPSS Windows) V.25 (IBM) and Stata V.15 (StataCorp, College Station, Texas).

RESULTS

A total of 2443 patients met the inclusion criteria of whom 900 (36.8%) had ongoing β- blocker therapy at the time of surgery. Six patients under 40 years of age were excluded per the study inclusion criteria. No patients were excluded due to a second operation during the 90-day postoperative follow-up period. No patients suffered simultaneous bilateral hip fractures. This level of drug exposure was in line with the proportion BB users in the general population in Örebro County, which was 36% for the same age group and time period as that of the current study cohort.[18] The Rikshöft registry had a coverage of 93% for hip fractures in Örebro County during the study period. All patients with BB therapy were continued on their normally prescribed BB agent throughout their hospital admissions.

In the BB (+) group, 595 (66.0%) patients were female compared with 1049 (68.0%) patients in the control group (p=0.341). Patients in the BB (+) group were significantly older (83 (SD 8) years vs. 81 (SD 11) years, p<0.001), less fit for surgery based on their American Society of Anesthesiologists classification (64.6% vs. 43.2% with ASA ≥3, p<0.001) and had a higher rate of comorbidities (80% vs. 61% with CCI ≥5, p<0.001). There were no statistically significant differences in the type of hip fracture or choice of surgical technique between groups (table 1).

Furthermore, the BB (+) group had a higher prevalence of patients with a history of myocardial infarction (27.7% vs. 8.5%, p<0.001), heart failure (32.8% vs. 8.5%, p<0.001) and peripheral vascular disease (11.6% vs. 4.9%, p<0.001) prior to surgery. The prevalence of cerebrovascular disease, chronic kidney disease and diabetes was also significantly higher in the BB (+) group. There were more patients with dementia in the BB (−) group compared with the BB (+) group (26.2% vs. 18.8%, p<0.001) (table 2).

Crude mortality was higher for both 30-day (9.1% vs. 7.7%) and 90-day mortality (16.1% vs. 13.5%) in the BB (+) cohort. These differences were statistically non-significant (table 3).

Multiple regression analysis found increasing age, ASA classification, increasing comorbidity burden, and male sex to be

Table 1 Patient demographics and clinical characteristics in β-blocker unexposed (BB−) and β-blocker exposed (BB+) patients undergoing surgery for hip fracture

	BB−	BB+	
	n=1543	n=900	P value
Age in years, mean (SD)	81.1 (10.6)	83.4 (8.3)	<0.001
Sex, n (%)			0.34
Female	1049 (68.0)	595 (66.1)	
Male	494 (32.0)	305 (33.9)	
Type of β-blocker, n (%)			–
Atenolol	–	209 (23.2)	
Bisoprolol	–	293 (32.6)	
Metoprolol	–	350 (38.9)	
Other	–	48 (5.3)	
ASA classification, n (%)			<0.001
1	160 (10.4)	24 (2.8)	
2	709 (45.9)	292 (32.4)	
3	591 (38.3)	472 (52.4)	
4	75 (4.9)	110 (12.2)	
Missing	8 (0.5)	2 (0.2)	
Charlson Comorbidity Index, n (%)			<0.001
≤4	603 (39.1)	180 (20.0)	
5–6	584 (37.8)	338 (37.6)	
≥7	356 (23.1)	382 (42.4)	
Fracture type, n (%)			0.13
Non-displaced cervical (Garden 1–2)	213 (13.8)	108 (12.0)	
Displaced cervical (Garden 3–4)	565 (36.6)	307 (34.1)	
Basicervical	72 (4.7)	39 (4.3)	
Pertrochanteric (two fragments)	361 (23.4)	226 (25.1)	
Pertrochanteric (multiple fragments)	237 (15.4)	142 (15.8)	
Subtrochanteric	95 (6.2)	78 (8.7)	
Type of surgery, n (%)			0.22
One screw or pin	2 (0.1)	2 (0.2)	
Two screws or pins	322 (20.9)	162 (18.0)	
Three screws or pins	2 (0.1)	1 (0.1)	
Screws or pins with side plate	546 (35.4)	336 (37.3)	
Intramedullary rod	239 (15.5)	162 (18.0)	
Hemiarthroplasty	309 (20.0)	182 (20.2)	
Total hip replacement	123 (8.0)	55 (6.1)	

ASA, American Society of Anesthesiologists; SD, Standard deviation.

Table 2 Preoperative comorbidities in β-blocker unexposed (BB–) and β-blocker exposed (BB+) patients undergoing surgery for hip fracture

	BB–	BB+	
	n=1543	n=900	P value
Myocardial infarction, n (%)	131 (8.5)	249 (27.7)	<0.001
Heart failure, n (%)	131 (8.5)	295 (32.8)	<0.001
Peripheral vascular disease, n (%)	76 (4.9)	104 (11.6)	<0.001
Cerebrovascular event, n (%)	311 (20.2)	284 (31.6)	<0.001
Dementia, n (%)	405 (26.2)	169 (18.8)	<0.001
Chronic obstructive pulmonary disease, n (%)	135 (8.7)	88 (9.8)	0.39
Connective tissue disease, n (%)	30 (1.9)	10 (1.1)	0.11
Peptic ulcer disease, n (%)	144 (9.3)	105 (11.7)	0.06
Liver disease, n (%)	22 (1.4)	9 (1.0)	0.36
Diabetes mellitus, n (%)			<0.001
Uncomplicated	93 (6.0)	68 (7.6)	
End-organ damage	84 (5.4)	127 (14.1)	
Hemiplegia, n (%)	38 (2.5)	31 (3.4)	0.15
Chronic kidney disease, n (%)	62 (4.0)	115 (12.8)	<0.001
Cancer, n (%)			0.33
Local tumor	297 (19.2)	189 (21.0)	
Metastatic	41 (2.7)	30 (3.3)	
Leukemia, n (%)	9 (0.6)	8 (0.9)	0.38
Lymphoma, n (%)	7 (0.5)	6 (0.7)	0.48

associated with increased 90-day mortality risk (table 4). After adjustments for clinically relevant variables, the Poisson regression model demonstrated a statistically significant 18% risk reduction for 90-day mortality (adjusted IRR 0.82, 95% CI 0.68 to 0.98, p=0.03) (table 4). Regression analysis for 30-day mortality revealed a non-significant trend towards decreased mortality risk in BB (+) patients (adjusted IRR 0.79, 95% CI 0.60 to 1.03, p=0.07) (table 3).

DISCUSSION

This is the first study investigating the association between β-adrenergic blockade and mortality after surgery for traumatic hip fractures. Our results show a significant risk reduction in 90-day mortality for patients who had ongoing BB therapy, after adjusting for relevant patient and clinical variables.

Both traumatic injury and surgical trauma are responsible for several physiological responses that are characterized by the activation of the sympathetic nervous system and mediated through the release of catecholamines. Although a necessary physiological response, the trauma-induced hyperadrenergic state may have prolonged or unwanted end-organ effects which could affect clinical outcomes. The most pronounced end-organ effect of adrenergic hyperactivity is seen on the cardiovascular system and can lead to cardiac complications such as arrhythmias or myocardial infarction specially in patients with prior heart disease.[19] Several studies show that adverse cardiovascular events are a common cause of death in patients undergoing surgery for hip fractures.[2 20 21] In cardiac surgery, there is strong evidence (level 1a) for the protective effects of β-blockade

Table 3 Outcomes in β-blocker unexposed (BB–) and β-blocker exposed (BB+) patients undergoing surgery for hip fracture

	BB–	BB+	
	n=1543	n=900	P value
Hospital length of stay (days)			<0.001
Mean (SD)	8.5 (5.8)	9.8 (6.5)	
Median (IQR)	7 (5, 11)	9 (5, 12)	
30-day mortality, n (%)	119 (7.7)	82 (9.1)	0.22
90-day mortality, n (%)	209 (13.5)	145 (16.1)	0.08
Adjusted IRR*			
30-day mortality, IRR (95% CI)	Ref	0.79 (0.60 to 1.03)	0.07
90-day mortality, IRR (95% CI)	Ref	0.82 (0.68 to 0.98)	0.03

*Poisson regression model with robust standard errors, multiple imputation was used for missing values. Model adjusted for age, sex, Charlson Comorbidity Index, American Society of Anesthesiologists (ASA) classification, fracture type and type of surgery. Multiple imputation method for missing ASA values.
CI, Confidence interval; IQR, Interquartile range; IRR, incidence rate ratio; SD, Standard deviation.

Table 4 Incidence rate ratio (IRR) for 90-day mortality after surgery for hip fracture

Variable		IRR (95% CI)	P value
β-blocker therapy			
	No	Ref	
	Yes	0.82 (0.68 to 0.98)	0.03
Age		1.05 (1.04 to 1.07)	<0.001
Sex			
	Female	Ref	
	Male	1.49 (1.23 to 1.80)	<0.001
Charlson Comorbidity Index			
	≤4	Ref	
	5–6	2.03 (1.41 to 2.94)	<0.001
	≥7	2.87 (1.97 to 4.17)	<0.001
ASA classification			
	1	Ref	
	2	1.87 (0.79 to 4.46)	0.15
	3	2.92 (1.23 to 6.92)	0.01
	4	5.24 (2.16 to 12.73)	<0.001
Fracture type			
	Non-displaced cervical (Garden 1–2)	Ref	
	Displaced cervical (Garden 3–4)	1.07 (0.73 to 1.57)	0.72
	Basicervical	1.45 (0.80 to 2.63)	0.22
	Pertrochanteric (two fragments)	1.68 (0.98 to 2.86)	0.05
	Pertrochanteric (multiple fragments)	1.37 (0.79 to 2.38)	0.26
	Subtrochanteric	1.13 (0.58 to 2.21)	0.72
Type of surgery			
	Screws or pins	Ref	
	Screws or pins with side plate	0.87 (0.54 to 1.40)	0.56
	Intramedullary rod	0.84 (0.50 to 1.43)	0.52
	Hemiarthroplasty	0.95 (0.66 to 1.35)	0.75
	Total hip replacement	0.52 (0.23 to 1.20)	0.12

Poisson regression model with robust standard errors, multiple imputation was used for missing values. Model adjusted for age, sex, Charlson Comorbidity Index, ASA classification, fracture type and type of surgery. Multiple imputation method for missing ASA values.
ASA, American Society of Anesthesiologists; CI, Confidence interval.

with a decreased risk of postoperative complications and higher degree of survival.[6] According to universal guidelines set by the American Heart Association/American College of Cardiology and European Society of Cardiology, BB therapy should not be discontinued before or after either cardiac or non-cardiac surgery.[22 23]

Adrenergic hyperactivity also leads to an increase in the levels of growth hormone and antidiuretic hormone which affect the pancreatic release of glucagon and insulin with a net result of catabolic activity. This results in an increase in glucose levels and peripheral insulin resistance.[13–15] The immune response is altered with a net increase in the production of proinflammatory cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-α). If prolonged, this can lead to multiple organ injury and subsequent organ failure. Unregulated, the inflammatory response can predispose to sepsis and overwhelming, hard-to-control inflammatory conditions.[13 14] BB therapy has shown an association with reduced mortality in patients suffering from sepsis.[24] A systematic review by Tan *et al*, including nine studies with a total of 56 414 patients, investigated the effect of β-blockade on sepsis. The results of this systematic review suggest that BB therapy, prior to developing full-blown sepsis, is associated with significantly reduced mortality.[24] Both in vivo and in vitro studies have shown that β-blockade downregulates the degree of circulating proinflammatory factors IL-6 and TNF-α, which could explain the drug's beneficial use in acting as an inflammatory balancing agent.[12 13 25]

A hyperadrenergic reaction after hip fractures, as with other traumatic injuries, is expected and could have the same devastating effects on outcomes. β-blockade therapy has previously shown an association with reduced mortality in patients suffering from non-orthopedic traumatic injury. Traumatic brain injury (TBI) is well known for inducing a hyperadrenergic state and is strongly associated with extracranial complications. Most notably are those of cardiac and pulmonary nature which underlie a large extent of the high mortality seen in brain injury victims.[26 27] Mohseni *et al* studied the effect of β-blockade on survival after isolated severe TBI and detected a significant decrease in mortality in patients who had an ongoing BB therapy prior to their TBI (adjusted OR=0.29, 95% CI 0.14 to 0.60, p=0.001).[8] A recent published prospective randomized controlled trial by Khalili *et al* showed the same positive results in patients with isolated severe TBI who received early BB.[9] Bukur *et al* also reported similar positive results in a study on critically ill trauma patients without severe head injuries.[7]

In addition, similar adverse effects of adrenergic hyperactivity are seen in major non-cardiac surgery.[15] BB therapy has also been shown to be protective and associated with better overall outcomes after major surgery.[6] A study by Lindenauer *et al*, consisting of almost 800 000 patients undergoing intrathoracic, intraperitoneal and suprainguinal vascular procedures, showed reduced in-hospital mortality in patients on BB therapy.[19] Ahl and colleagues conducted a study on patients undergoing emergency surgery for colon cancer and showed a significant increase in survival up to 1 year postoperatively in BB-treated patients (adjusted HR=0.40, 95% CI 0.26 to 0.62, p<0.001).[10] The same positive results were obtained when looking at mortality after rectal cancer surgery.[11]

Patients incurring hip fractures are known to be older and have a higher comorbidity burden. This predisposes them to worse outcomes.[2 20 21 28 29] A recent study by Gundel *et al*, which used data from Denmark's national register, included 113 957 patients with a hip fracture during a 15-year period. They found 9.6%, 16%, and 27% postoperative mortality rates after surgery at 30 days, 90 days and 1 year, respectively. Interestingly, the authors did not find any trend towards an increase or decrease in mortality during the 15-year study period despite national efforts to improve overall outcomes with the implementation of orthogeriatric collaborations and fast-track surgery during the last decade.[2 5] Overall 30-day and 90-day mortality in our cohort were 8.2% and 14.5%, respectively. Previous studies have reported male sex, increasing age and increasing CCI to be significant risk factors for mortality after surgery for hip fractures.[2] In the current study, male sex, increasing age, ASA classification, and comorbidities were also significant risk factors for 90-day mortality. After adjusting for clinically relevant risk factors, an 18% reduction in the incidence of 90-day postoperative mortality was detected in the current study (adjusted IRR 0.82, 95% CI 0.68 to 0.98, p=0.03). There was no significant protective effect seen in the immediate (30-day) postoperative period. One possible explanation for this discrepancy could be if there were a higher rate of *do not resuscitate* or *limited advance directives* in patients on BB therapy. This would not be surprising since the BB group was significantly older, had higher ASA classification scores, and had a higher comorbidity burden. This is, however, purely a possible hypothesis by the authors and cannot be supported by data due to the lack of patient information regarding resuscitative status in the event of cardiac arrest nor restriction of care.

The strength of the current study is founded in the use of a prospectively collected database with access to in-hospital medical records. However, there are important limitations to the current study. The inclusion of patients is limited to one university hospital and two university-affiliated hospitals. This could affect the generalizability of the results. Although the Rikshöft registry is a prospectively collected database, the coverage was limited to 93% in the studied county. Although electronic medical records were reviewed for continuation of preadmission BB therapy, no attempt was made to collect data concerning changes in dosage or missing doses during the hospital stay. Further, type of anesthesia, postoperative complications, or organ failures requiring invasive support such as mechanical ventilation or dialysis, were not collected in the current database. Additionally, cause-specific mortality could not be recorded due to the fact that the majority of deaths occurred after discharge from the hospital.

CONCLUSION

The results of this observational study support a potential protective role of early β-blockade in patients undergoing surgery for hip fractures. This finding warrants further investigation.

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