Hypertension Research (2024) 47:796–798
https://doi.org/10.1038/s41440-023-01546-x

COMMENT

Anti-adrenergic agents and the risk of postoperative acute kidney injury

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Received: 9 November 2023 / Accepted: 14 November 2023 / Published online: 22 December 2023

Keywords adrb2 · AKI · Anti-adrenergics

Acute kidney injury (AKI) has been on the rise, attributed to multiple factors, such as an aging society, the increasing complexity of medical technology, and the increase in lifestyle-related diseases [1]. AKI causes deterioration in renal function and is associated with increased mortality in the short and long term [2]. Currently, the Kidney Disease: Improving Global Outcomes (KDIGO) criteria has widely been used to define AKI, which combined the RIFLE criteria by the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN) criteria [3]. In the KDIGO criteria, AKI is defined by the degrees of absolute serum creatinine increase, of percent serum creatinine increase, or decrease in urine output, and is further classified into three stages. Accumulating data have shown that the patients with AKI defined using this criteria show increased in-hospital mortality compared to non-AKI patients [4]. In addition to the short-term outcomes, AKI influences long-term effects; several studies have shown that AKI is associated with chronic kidney disease progression, cardiovascular events, and mortality in the long term [5]. Therefore, prediction, prevention, and early diagnosis of AKI are important challenges to overcome.

Previous studies have identified various risk factors to predict the occurrence of AKI in different clinical settings. These include reduced renal function, heart failure, diabetes mellitus, number of blood products infused during operation, and older age [6–8]. Among the antihypertensive medications, several lines of evidence indicate that using angiotensin-converting enzymes or angiotensin II receptor blockers is associated with increased frequency of AKI [9, 10]. However, the association between anti-adrenergic drugs and postoperative AKI remained undetermined.

In the NARA-AKI Cohort Study, Nishimoto et al. [11] addressed whether the use of anti-adrenergic agents (α-blockers, β-blockers, or both) is associated with AKI in patients undergoing non-cardiac surgery. The NARA-AKI Cohort study was a single-center, retrospective cohort study that included patients who ≥ 18 years old and receiving non-cardiac surgery under general anesthesia from 2007 to 2011 at Nara Medical University. Patients with preoperative dialysis, obstetric, or urological surgery were excluded. The exposure of interest was the regular use of α-blockers and β-blockers before operation. The definition of AKI was in accordance with the KDIGO criteria, and postoperative AKI within 1 week as well as trajectories of eGFR were analyzed.

Among 5168 patients who were eligible for analysis, 245 patients (4.7%) were regularly taking anti-adrenergic agents before surgery. Patients who were taking anti-adrenergic agents were older, had lower eGFR, and higher blood pressure (BP) levels at baseline. Overall, AKI after the surgery occurred in 309 patients (6.0%). The study found that the use of anti-adrenergic agents was significantly associated with postoperative AKI (unadjusted odds ratio, 2.83 [interquartile ranges, 1.94−4.13]), and that this association was significant after adjustment of potential confounders, including age, eGFR, pre-existing cardiovascular diseases, intraoperative vasopressors, and other antihypertensive medications [11]. Among the 309 patients who had postoperative AKI, 35 patients were taking anti-adrenergic agents, whereas 274 patients were not. The authors further compared the trajectories of eGFR levels after AKI and found that the recovery of kidney function after AKI was delayed in patients with anti-adrenergic agents [11]. Thus, the use of anti-adrenergic agents is

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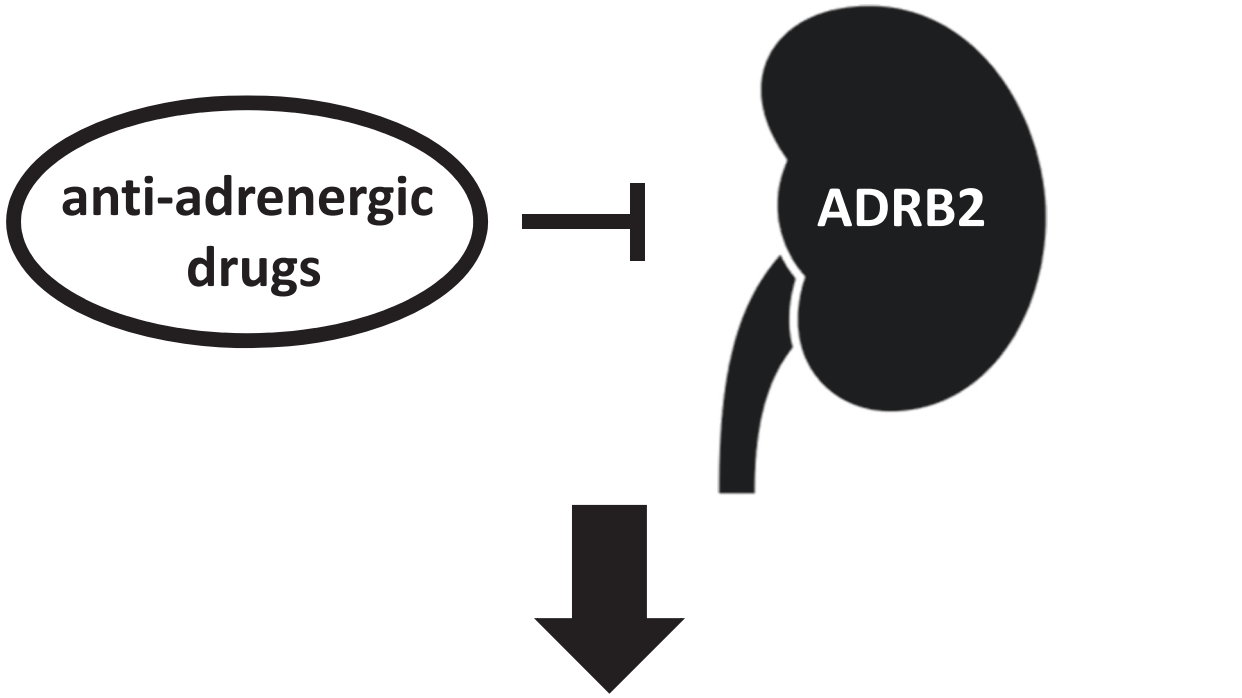
Graphical Opinion



considered an additional risk factor after non-cardiac surgery in this cohort, independently of other conditions.

As a possible explanation for the association of anti-adrenergic drugs with postoperative AKI, the authors speculated the role of β2 adrenergic receptor (Adrb2), a G protein-coupled receptor. Upon binding catecholamines, Adrb2 mainly signals through stimulatory G protein (Gs), which activates adenylyl cyclase and cyclic-AMP-dependent pathway and also induces inhibitory G protein (Gi) signaling [12]. Although the precise distribution of Adrb2 within the kidney is not entirely solved, studies have shown that it is present in various cells, including vascular smooth muscle cells, glomerular cells, proximal tubule cells, and immune cells [13, 14]. It has also been reported that several pathological conditions, such as sepsis and heart failure, can impair β-adrenergic receptor signaling [15, 16].

Experimental studies indicate that Adrb2 signaling has a protective effect in rodent models of AKI. In a lipopolysaccharide (LPS)-induced AKI model, Nakamura et al. showed that renal function decline and leukocyte infiltration were significantly reduced by the adenoviral delivery of human ADRB2 to the kidney [17]. Conversely, renal injury induced by acute renal infection was aggravated by a β2 adrenergic receptor antagonist [18]. Of further note, intraperitoneal injection of formoterol, a specific long-acting β2 adrenergic receptor agonist, has also been shown to rescue renal tubules from ischemia/reperfusion-induced injury [19]. Formoterol has also been shown to promote mitochondrial biogenesis [20], likely contributing to renal function recovery after AKI induced by ischemia/reperfusion [19]. These data can be relevant to the clinical study by Nishimoto et al. [11], providing possible mechanisms for the observed association.

The study by Nishimoto et al. also showed that the recovery of renal function was slower in patients taking anti-adrenergic agents [11]. Currently, time from onset to recovery is not included in the grade severity of AKI in the KDIGO classification. However, it is plausible that the duration of AKI has an additional predictive value. Indeed, a meta-analysis indicated that the period of AKI was independently associated with long-term outcomes. In that study, long-term mortality was higher for longer AKI duration in each stage of AKI [21]. In addition to this study, recent research on AKI in patients with coronavirus disease

19 [22] and those receiving vascular surgery [23] showed that persistent AKI predicts mortality, supporting the prognostic importance of AKI duration.

In summary, the study by Nishimoto et al. showed that the use of anti-adrenergic agents was significantly associated with postoperative AKI and the delayed recovery of renal function, unveiling an additional risk factor of post-operative AKI. As a future study, it would be informative to evaluate whether the types and dosages of anti-adrenergic agents alter the risk. Also, given the experimental evidence that Adrb2 is involved in sepsis and ischemia/reperfusion injury, it may be worth evaluating whether the use of anti-adrenergic agents is associated with AKI in these conditions, in addition to the post-operative AKI.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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