Review
Pregledni članak

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The influence of ondansetron on hemodynamic stability after subarachnoid anesthesia in the elderly: a narrative review article

Utjecaj ondansetrona na hemodinamsku stabilnost nakon subarahnoidne anestezije u starijih osoba: narativni pregledni članak

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Summary

Background: Spinal anesthesia (SA) is widely utilized in elderly patients due to its benefits, such as reduced postoperative morbidity and decreased opioid requirements. Despite these advantages, SA-induced hypotension (SAIH) is a significant concern, especially in geriatric patients with compromised cardiovascular function. The Bezold-Jarisch reflex (BJR), which mediates bradycardia and hypotension, plays a crucial role in SAIH.

Objective: This review aims to evaluate the effectiveness of prophylactic intravenous ondansetron in preventing hypotension and a decrease in cardiac output following SA in elderly patients undergoing elective surgery.

Mechanism of Action: Ondansetron, a 5-HT3 receptor antagonist, is commonly used to prevent nausea and vomiting. However, 5-HT3 receptors also participate in cardiovascular reflexes, particularly in the activation of BJR, leading to hemodynamic instability. By blocking these receptors, ondansetron may mitigate the incidence of SAIH by reducing vagally mediated bradycardia and vasodilation.

Clinical Evidence: Numerous studies have investigated the role of ondansetron in stabilizing blood pressure and heart rate after SA. While earlier trials primarily focused on obstetric populations, recent research suggests that ondansetron effectively reduces SAIH, bradycardia, and vasopressor requirements in elderly patients undergoing non-obstetric surgeries. A mixed-population meta-analysis of 25 randomized controlled trials confirmed ondansetron's ability to reduce the incidence of SAIH and bradycardia, with a decreased need for vasopressor interventions.

Conclusion: Current evidence suggests that prophylactic ondansetron administration may enhance hemodynamic stability in elderly patients undergoing SA, potentially reducing the need for vasopressor support. Further large-scale studies are required to establish standardized dosing protocols and confirm long-term benefits in this population.

Key words: ondansetron, hypotension, spinal anesthesia, elderly.

Sažetak

Pozadina: Spinalna anestezija (SA) široko se koristi kod starijih bolesnika zbog svojih prednosti, kao što su smanjeni postoperativni morbiditet i smanjena potreba za opioidima. Unatoč tim prednostima,

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hipotenzija izazvana SA (SAIH) predstavlja značajnu zabrinutost, posebno kod gerijatrijskih bolesnika s kompromitiranom kardiovaskularnom funkcijom. Bezold-Jarischov refleks (BJR) koji posreduje u bradikardiji i hipotenziji igra ključnu ulogu u SAIH.

Cilj: Cilj ovoga pregleda je procijeniti učinkovitost profilaktičkog intravenskog ondansetrona u sprječavanju hipotenzije i smanjenja srčanog minutnog volumena nakon SA kod starijih bolesnika koji se podvrgavaju elektivnoj operaciji.

Mehanizam djelovanja: Ondansetron, antagonist 5-HT3 receptora, često se koristi za sprječavanje mučnine i povraćanja, no međutim, 5-HT3 receptori također sudjeluju u kardiovaskularnim refleksima, posebno u aktivaciji BJR-a, što dovodi do hemodinamske nestabilnosti. Blokiranjem ovih receptora ondansetron može ublažiti učestalost SAIH smanjenjem vagusno posredovane bradikardije i vazodilatacije.

Klinički dokazi: Brojne studije istraživale su ulogu ondansetrona u stabilizaciji krvnoga tlaka i otkucaja srca nakon SA. Dok su se ranija ispitivanja prvenstveno usredotočila na opstetričke populacije, nedavna istraživanja sugeriraju da ondansetron učinkovito smanjuje SAIH, bradikardiju i potrebe za vazopresorima kod starijih bolesnika koji se podvrgavaju neopstetričkim operacijama. Meta-analiza mješovite populacije koja je uključivala 25 randomiziranih kontroliranih ispitivanja potvrdila je sposobnost ondansetrona da smanji incidenciju SAIH i bradikardije, sa smanjenom potrebom za vazopresorskim intervencijama.

Zaključak: Trenutni dokazi upućuju na to da profilaktička primjena ondansetrona može poboljšati hemodinamsku stabilnost kod starijih bolesnika koji se podvrgavaju SA, potencijalno smanjujući potrebu za vazopresorskom potporom. Potrebna su daljnja opsežna istraživanja kako bi se utvrdili standardizirani protokoli doziranja i potvrdile dugoročne koristi u ovoj populaciji.

Ključne reči: ondansetron, hipotenzija, spinalna anestezija, stariji.

Background

Spinal anesthesia (SA) is widely used in elderly patients because it lowers postoperative morbidity and reduces the need for systemic opioids.[1,2]

Over the past two decades, the use of spinal anesthesia (SA) for hip fracture repair has increased worldwide.[3,4] SA is associated with improved short-term outcomes, including a reduced hospital length of stay and fewer cardiopulmonary complications, particularly in frail and elderly patients.[5-7] However, it does not appear to affect long-term morbidity or mortality.[3-8] Despite these benefits, SA carries significant risks, most notably hypotension and bradycardia, which can be especially hazardous in elderly patients with compromised cardiovascular reserve. A recent systematic review and meta-analysis support the use of neuraxial over general anesthesia for primary unilateral total hip arthroplasty.[9] SA, achieved by blocking preganglionic sympathetic fibers, provides favorable modulation of the surgical stress response.[10-12] Nevertheless, arterial hypotension remains a frequent adverse effect.[13] In elderly patients, the incidence of spinal anesthesia-induced hypotension (SAIH) approaches 80%.[14] driven by reductions in both systemic vascular resistance (SVR) and cardiac output (CO).[10] Given the high prevalence of comorbidities in this population, the risk of hypoperfusion is particularly pronounced.[10,15,16]

As the mechanism of SAIH involves the reduction in vascular resistance caused by the sympathetic block and the activation of the Bezold–Jarisch reflex (BJR), it leads to vasodilation and hypotension.[17] The BJR is activated by peripheral serotonin receptors, 5-Hydroxytryptamine3 (5HT3)[18] which antagonist was reported to suppress bradycardia and hypotension by preventing the Bezold–Jarisch reflex in a rabbit model[19], but also by 5-HT1B/1D, 5-HT7, and 5-HT2A/2B receptors.[20] The receptors that trigger the BJR are mechanoreceptors located in the heart walls. These receptors participate in systemic responses to hypervolaemia (“true” BJR) and hypovolaemia (pseudo BJR).[21] They also include chemoreceptors that are sensitive to serotonin (5-HT3 receptors).[22] Ondansetron has emerged as a potential agent for preventing these hemodynamic disturbances by inhibiting serotonin-mediated vagal reflexes and modulating sympathetic tone.[23] Numerous clinical trials have been performed to demonstrate the preventive effect of ondansetron on SAIH.[24-26] Seventeen trials (8 obstetric, 9 non-obstetric) were included in a meta-analysis published in 2016, which concluded that 5HT3 receptor antagonists effectively reduced the incidence of SAIH in obstetric patients but had no significant effect on the non-obstetric population.[27] Recently, a meta-analysis[28] showed that prophylactic administration of ondansetron results in the reduction of the incidence of SAIH, bradycardia, and rescue ephedrine in patients undergoing non-caesarean delivery under SA. The objective of this review is to evaluate the effectiveness of prophylactic intravenous (IV) ondansetron bolus application on the prevention of hypotension and the decrease in CO following SA in elderly patients undergoing elective surgery. Ondansetron's mechanism of action, with a good safety profile, encouraged clinical investigators to collect clinical evidence that shows promising

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The objective of this review is to evaluate the effectiveness of prophylactic intravenous (IV) ondansetron bolus application on the prevention of hypotension and a decrease in CO following SA in elderly patients undergoing elective surgery. Ondansetron's mechanism of action, with a good safety profile, encouraged clinical investigators to make clinical evidence that shows promising results in elderly patients.

Mechanism of Action

Ondansetron is a 5-HT3 receptor antagonist primarily used to prevent nausea and vomiting. Beyond this role, 5-HT3 receptors are also involved in cardiovascular reflexes, most notably the Bezold–Jarisch reflex (BJR), which contributes to bradycardia and hypotension.

The BJR is an inhibitory reflex originating from receptors located in the inferoposterior region of the left ventricle. The activation of these receptors by stretch, chemical mediators, or pharmacological agents increases parasympathetic activity and suppresses the sympathetic tone, thereby inducing hypotension, bradycardia, and coronary vasodilation.[29,30] The afferent pathway consists of unmyelinated type C vagal fibers, which mediate parasympathetic efferent discharge to the heart, leading to bradycardia and peripheral vasodilation.

This reflex is considered cardioprotective during profound reductions in cardiac filling, as it slows the heart to permit more complete ventricular filling. However, excessive activation may precipitate severe bradycardia or even asystole.[30] Accordingly, BJR has long been implicated in the cardiovascular collapse occasionally observed during spinal anesthesia. The initial hypotension following spinal anesthesia is largely attributable to sympathectomy and reduced systemic vascular resistance[31], while the subsequent decrease in venous return further activates ventricular chemoreceptors and mechanoreceptors, thereby reinforcing the BJR.[32]

The mechanism of the BJR activation is shown in Figure 1.

By blocking these receptors, ondansetron may attenuate the SAIH.

Clinical Evidence

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Cochrane Library, Web of Science, and Scopus databases to identify relevant clinical trials, meta-analyses, and reviews. Additional references were retrieved through manual searches of bibliographies and Google Scholar, all from 01.01.2000-01.05.2025 (Table 1).

Several studies have examined the role of ondansetron in stabilizing blood pressure and heart rate following spinal anesthesia (SA). Many of the randomized controlled trials (RCTs) were conducted in obstetric populations.[24-27] while others included non-obstetric patients.[27,28] However, the majority of these studies enrolled relatively young participants (generally ≤70 years), and their conclusions are therefore based primarily on non-elderly populations.

Ondansetron has been evaluated in intravenous doses ranging from 2 to 12 mg, typically administered five minutes before the induction of SA.[24-28] In obstetric trials, prophylactic ondansetron significantly reduced the incidence of spinal anesthesia-induced hypotension (SAIH) and bradycardia.[24-27] Evidence also suggests that in non-obstetric patients undergoing surgery other than cesarean delivery, ondansetron reduces the incidence of SAIH, bradycardia, and the requirement for rescue ephedrine.[28]

The most relevant clinical effects associated with ondansetron administration include the prevention of SAIH, the attenuation of bradycardia, and a reduction in fluid and vasopressor requirements[20-32], as illustrated in Figure 2. Preoperative administration of ondansetron, most often 4–8 mg intravenously, has consistently been shown to decrease both the incidence and the severity of SAIH.[27,28] The drug also appears to mitigate bradycardia, most likely through the inhibition of vagal tone.[23,32] Several studies further suggest that patients treated with ondansetron require lower doses of vasopressors (such as ephedrine or phenylephrine) and less fluid resuscitation compared with controls.[24-28]

Only a limited number of RCTs have specifically investigated the effect of ondansetron on SAIH in elderly patients. A Brazilian study[20] demonstrated that prophylactic ondansetron significantly reduced both the incidence of hypotension and the need for ephedrine in elderly patients undergoing non-obstetric surgery. Interestingly, the authors noted that older patients were at greater risk for hypotension and that ondansetron exerted a more pronounced protective effect in the elderly than in younger individuals.

Similarly, a small Polish study[33] reported that intravenous ondansetron attenuated the decrease in diastolic (DAP) and mean arterial pressure (MAP) during SA in geriatric patients, while systolic pressure (SAP) remained unaffected. In elderly patients, SA primarily reduces systemic vascular resistance (SVR) without altering cardiac output[34], which correlates closely with changes in DAP.

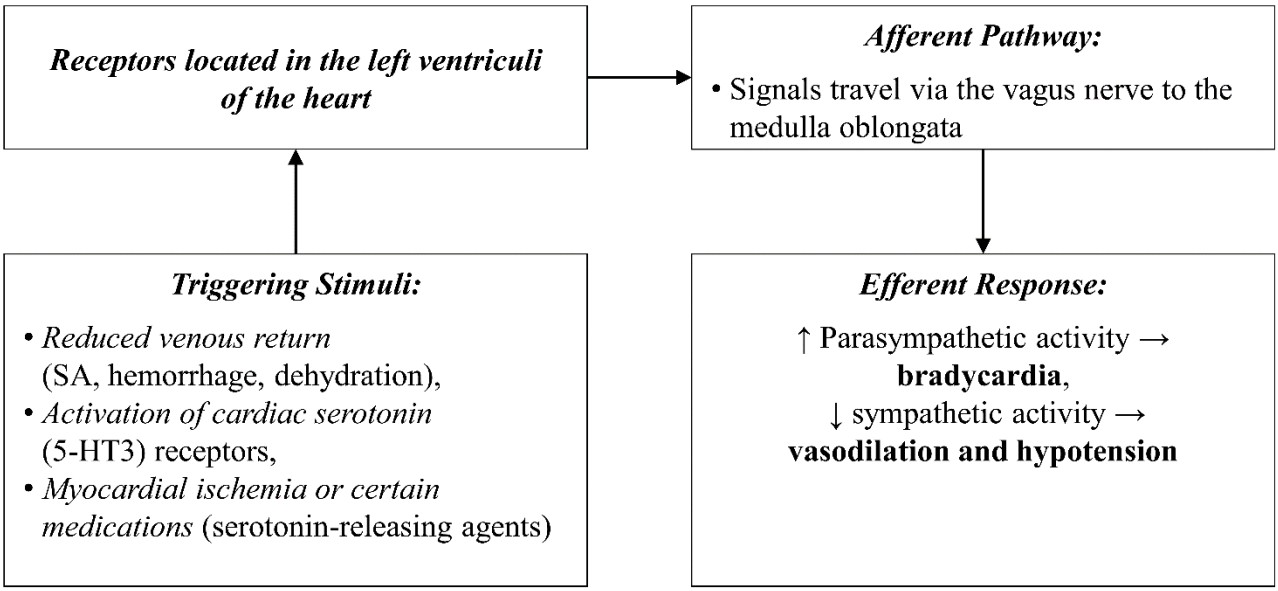

Figure 1 Bezold–Jarisch reflex (BJR) mechanism
Slika 1. Mehanizam Bezold–Jarischovog refleksa (BJR)

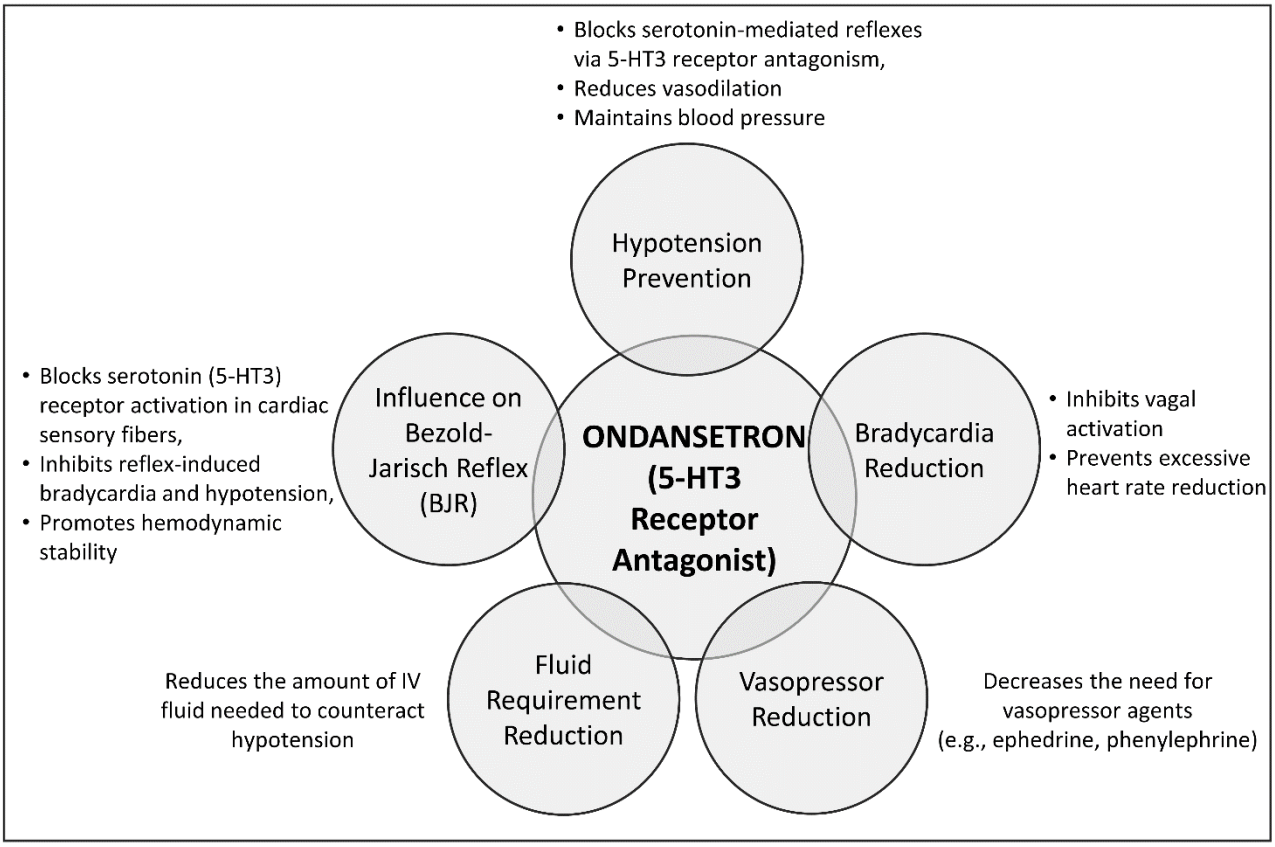

Figure 2 Clinical Effects of Ondansetron on Hemodynamic Stability
Slika 2. Klinički učinci ondansetrona na hemodinamsku stabilnost

Table 1 Summary of Randomized Controlled Trials and Meta-Analyses on Ondansetron for the Prevention of Spinal Anesthesia-Induced Hypotension (2000–2025)

Tablica 1. Sažetak randomiziranih kontroliranih ispitivanja i meta-analiza o ondansetronu za prevenciju hipotenzije izazvane spinalnom anestezijom (2000. – 2025.)

Year	**First author** *Prvi autor*	**Design** *Dizajn*	**Population/ Setting** *Stanovništvo Okruženje*	**Comparators / groups** *Komparatori / grupe*	***Age (mean/ range)*** *Dob (srednja /raspon)*	**Dose & timing (ondansetron)** *Doza i vrijeme primjene (ondansetron)*	**Primary outcome** *Primarni ishod*
2008	Owczuk R.	DB RCT	Adults undergoing SA (mixed surgeries) *Odrasli koji se podvrgavaju SA (mješovitim operacijama*)	8 mg IV OND vs P	Adults (not elderly-specific) *Odrasli (ne specifično za starije osobe)*	8 mg IV (before SA; exact timing not specified in abstract) *8 mg IV (prije SA; točno vrijeme nije navedeno u sažetku)*	Minimal SBP and MAP over 20 min; attenuation of BP drop *Minimalni sistolični krvni tlak (SBP) i srednji arterijski tlak (MAP) tijekom 20 minuta; slabljenje pada krvnog tlaka*
2012	Sahoo T.	DB RCT	Cesarean delivery (parturients) *Carski rez (partirenti)*	4 mg IV OND vs P	Reproductive-age parturients *Rodilje u reproduktivnoj dobi*	4 mg IV before SA *4 mg IV prije SA*	Incidence of SAIH *Incidencija SAIH*-a
2016	Heesen M.	SR MA (17 RCTs)	8 Obstetric & 9 non-obstetric RCTs *8 opstetričkih i 9 neopstetričkih RCT-ova*	5-HT3 antagonists vs P 5-HT3 *antagonisti u odnosu na P*	Varied across trials *Razlikovalo se među ispitivanjima*	2–12 mg IV across trials *2–12 mg intravenski u svim ispitivanjima*	Incidence of hypotension (primary outcome of meta-analysis) *Incidencija hipotenzije (primarni ishod meta-analize)*
2019	Tatikonda C.M.	DB RCT	Adults undergoing SA *Odrasle osobe pod SA*	OND vs P	Adults *Odrasli*	Dose per study protocol (IV) *Doza prema protokolu studije (IV)*	Attenuation of arterial BP drop after SA *Slabljenje pada arterijskog krvnog tlaka nakon SA*
2019	Shah S.A.R.	RCT (elderly) *(stariji)*	Elderly patients undergoing lower limb surgery *Stariji bolesnici koji se podvrgavaju operaciji donjih ekstremiteta*	OND IV 8 mg vs P	Geriatric patients *Gerijatrijski bolesnici*	8 mg IV prior to SA *8 mg IV prije SA*	Incidence of SAIH *Incidencija SAIH*-a
2020	Xiao F.	Prospective, R, DB	Cesarean delivery *Carski rez*	IV OND vs C	Parturients *Rodilje*	IV ondansetron (per protocol) *IV ondansetron (prema protokolu)*	Effect on phenylephrine ED50 and hemodynamic effects *Učinak na ED50 fenilefrina i hemodinamske učinke*
2021	Mendonça F.T.	R, DB, PC	Non-obstetric surgeries (including elderly)	OND vs P	Elderly cohort included	IV ondansetron (per protocol, e.g., 4–8 mg)	Incidence of SAIH and vasopressor use *Incidencija SAIH-a i upotrebe vazopresora*

Year	First author *Prvi autor*	Design *Dizajn*	Population/ Setting *Stanovništvo Okruženje*	Comparators / groups *Komparatori / grupe*	*Age (mean/ range)* *Dob (srednja /raspon)*	Dose & timing (ondansetron) *Doza i vrijeme primjene (ondansetron)*	Primary outcome *Primarni ishod*
			Neopstetričke operacije (uključujući starije osobe)		*Uključena starija kohorta*	*IV ondansetron (prema protokolu, npr. 4–8 mg)*	
2022	Hou X-M.	SR MA (25 RCTs)	RCTs across obstetric and non-obstetric *RCT-ovi u opstetričkoj i neopstetričkoj medicini*	OND vs C	Varied *Razno*	Mostly 4–8 mg IV prior to SA *Uglavnom 4–8 mg IV prije SA*	Incidence of hypotension after SA *Učestalost hipotenzije nakon SA*

PC-placebo-controlled; C-control; R-Randomized; OND-ondansetron; P-placebo; DB-double-blind; RCT-randomised controlled trial; IV-intravenously; MA-meta-analysis; SR-systematic review
PC-place kontrolirano; C-kontrola; R-randomizirano; OND-ondansetron; P-placebo; DB-dvostruko slijepo; RCT-randomizirano kontrolirano ispitivanje; IV-intravenozno; MA-meta analiza; SR-sitematski pregled

Thus, ondansetron's protective action in this cohort was confined to DAP and MAP. This finding differs from studies in mixed populations[35] and obstetric patients[36], where ondansetron significantly influenced SAP as well. Other small RCTs[37,38] have corroborated these observations.

A recent meta-analysis[39], including 25 RCTs with 2,536 participants (1,405 ondansetron, 1,131 control), concluded that ondansetron significantly reduced the incidence of SAIH and bradycardia, along with lowering vasopressor use and cumulative ephedrine dose.

In addition to its hemodynamic effects, ondansetron may also provide neurocognitive benefits. Furthermore, Papadopoulos et al.[40] reported that prophylactic administration of ondansetron protected and potentially improved postoperative cognitive function in elderly orthopedic patients undergoing general anesthesia.

Considerations in Elderly Patients

Old age is characterized by a progressive decline in adaptive capacity. Elderly individuals commonly display altered autonomic responses and heightened sensitivity to hemodynamic fluctuations.[41] In this population, chronic inflammation, oxidative stress, and endothelial dysfunction contribute to increased arterial stiffness and reduced vascular distensibility. These changes result in elevated systolic arterial pressure (SAP) and pulse pressure, enhanced left ventricular contraction and afterload, and impaired coronary perfusion with reduced early diastolic filling.[42]

Aging is also associated with diminished responsiveness to beta-adrenergic stimulation and a relative increase in parasympathetic activity, which attenuates both cardiopulmonary and baroreflex mechanisms.[43] The combination of vascular stiffness and vasodilation induced by a neuraxial block produces a significant reduction in preload in geriatric patients, which may explain the heightened activity of the Bezold–Jarisch reflex (BJR) in this population.[20]

The management of perioperative hypotension in the elderly is further complicated by comorbidities. A routine crystalloid infusion may precipitate fluid overload and heart failure, while prophylactic vasopressors are inconsistently effective and may cause excessive hypertension and tachycardia.[44-46] Moreover, alpha-agonists are often contraindicated due to the risk of cardiovascular decompensation.

In this context, ondansetron represents a promising adjunct. By stabilizing blood pressure without inducing marked tachycardia or vasoconstriction, it potentially offers a safer option for elderly patients. Nevertheless, its efficacy may vary depending on comorbidities, baseline autonomic function, and concurrent medication use.

Safety and Adverse Effects

Ondansetron is generally well-tolerated, with minimal cardiovascular side effects. However, potential concerns include QT interval prolongation, which should be considered in elderly patients with preexisting cardiac conditions. Ondansetron should be used with caution in patients who have

experienced or may experience QT prolongation; these include patients with electrolyte disturbances, congestive heart failure, bradycardia and users of other medications that cause QT prolongation or electrolyte disturbances.[47]

Conclusion

Current evidence supports the role of ondansetron in improving hemodynamic stability following SA in elderly patients. By reducing the incidence of hypotension and bradycardia, ondansetron may enhance perioperative safety and reduce the need for vasopressor interventions. Further large-scale studies are needed to establish standardized dosing protocols and confirm long-term benefits.

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