Hyponatremia After Primary Hip and Knee Arthroplasty: Incidence and Associated Risk Factors

Alexander P. Sah, MD

Abstract

Hyponatremia is the most common electrolyte abnormality in clinical practice. Often overlooked or misdiagnosed, hyponatremia can quickly deteriorate and cause serious and potentially life-threatening complications. In the orthopedic patient, hyponatremia can mimic common postoperative sequelae, thereby making diagnosis even more difficult. Although serious complications of hyponatremia are rare, they are severe, and early detection is crucial in initiating prompt treatment.

From 2008 to 2010, 392 consecutive hip and knee arthroplasties were prospectively monitored for development of hyponatremia. Hyponatremia occurred in 155 (40%) of cases. Although the majority were mild, 7% were moderate or severe deficiencies, which are associated with increased morbidity. Risk factors included preoperative hyponatremia, female sex, older age, lower body weight, knee more than hip surgery, and bilateral knee arthroplasty. Thiazides and angiotensin-converting enzyme inhibitors were the only medications associated with low postoperative sodium values.

Hyponatremia is common after elective orthopedic surgery and is associated with identifiable perioperative risk factors. Although the most severe complications are rare, failure to identify mild cases of hyponatremia allows the sodium deficit to worsen unnecessarily. Early detection is important because, unlike severe cases, mild hyponatremia is generally treatable with simple medical management.

Hyponatremia is the most common electrolyte abnormality in hospitalized patients.[1-3] Fluid shifts and electrolyte changes occur after surgical procedures, including total hip and knee arthroplasties.[4,5] There are few published data on the overall incidence of this postoperative abnormality, either in general, or in this specific orthopedic population. Severe hyponatremia is reported to occur in 5% to 7% of hospitalized patients.[6] These cases of severe hyponatremia may be better avoided if smaller decreases in sodium levels are identified more promptly. However, routine laboratory work to detect this electrolyte deficiency is often not ordered, and, when the deficiency is identified, it is often disregarded.[6,7] Because of the insidious nature of hyponatremia, early and less severe manifestations can quickly progress into serious and potentially life-threatening complications.

Hyponatremia can cause a wide spectrum of symptoms, including headache, lethargy, nausea, weakness, agitation, anorexia, slurred speech, and confusion.[1,2] Specific to the rehabilitation of the orthopedic patient, even mild hyponatremia is associated with attention impairment, gait instability, and falls.[8] These symptoms are often encountered in postoperative patients and can often be mistakenly disregarded as common postoperative sequelae or attributed to narcotics or residual anesthetic effects. For example, the reported incidence of postoperative nausea and vomiting after lower extremity joint arthroplasty is 20% to 83%.[9-11] In some cases, hyponatremia may be the true cause of these symptoms, and failure to identify the electrolyte abnormality may allow it to worsen unnecessarily.[6] Severe hyponatremia must be avoided because it is associated with a very poor prognosis.[7] Symptoms can cause reactions mimicking stroke or lead to seizures, neurologic damage, coma, and even death.[2]

A study was conducted to evaluate a consecutive series of elective hip and knee arthroplasties for development of postoperative hyponatremia. Awareness of risk factors may enhance the ability to identify patients susceptible to postoperative sodium deficiency and lead to more prompt treatment. Understanding the frequency and potential severe clinical manifestations of hyponatremia may encourage improved recognition and management of this generally easily treated postoperative disorder.

Materials and Methods

From 2008 to 2010, 392 consecutive hip and knee arthroplasties were prospectively monitored for development of hyponatremia.

Author's Disclosure Statement: The author reports no actual or potential conflict of interest in relation to this article.

Demographic data are listed in **Table I**. There were 253 knee arthroplasties (184 unilateral, 4 revision, 9 partial, 56 bilateral) and 139 hip arthroplasties (133 primary, 6 revision). Patient data for medications prescribed, intraoperative and postoperative intravenous (IV) fluid intake, oral fluid intake, and urine output were recorded. Electrolyte levels were measured before surgery, in the recovery room immediately after surgery, each postoperative day, and, if necessary, after hospital discharge.

Hyponatremia was defined as a level less than 135 mmol/L (mild, ≥ 130 mmol/L; moderate, ≥ 125 mmol/L; severe, < 125 mmol/L). All hyponatremia values were also adjusted based on elevated glucose levels to determine true sodium levels. Potassium and creatinine levels were evaluated and deficiencies recorded.

In all cases, the intraoperative fluid given by the anesthesia service was lactated Ringer's solution. Postoperative maintenance IV fluid was normal saline, and infusion rate was based on patient weight. Total fluid intake was monitored both intravenously and orally each day. Fluid output was accordingly recorded each day with fluid balance calculated per 24 hours.

Identification of hyponatremia prompted a mild restriction in oral fluid, 1000 mL per 24 hours. Patient oral intake of fluids with electrolytes, rather than free water, was encouraged until sodium level normalized. Thiazides and angiotensin-converting enzyme (ACE) inhibitors were temporarily held during this period, per the literature.[3,12] For resistant or worsening cases of hyponatremia, gentle normal saline infusion and diuresis with furosemide were performed. Patients with unresolved hyponatremia at discharge had their electrolyte levels monitored on an outpatient basis until levels normalized.

Student *t* test and χ^2 test were used with significance set at $P < .05$. Student *t* test was used to evaluate the statistical significance of perioperative fluid intake, urine output, and fluid balance between groups. Chi-square test was used to evaluate the association of group characteristics with occurrence of hyponatremia.

Results

Hyponatremia occurred in 155 (40%) of the 392 hip and knee arthroplasties. In contrast, hypokalemia occurred in 52 patients (15%), and creatinine was elevated in 36 patients (9%). There were 127 mild cases, 22 moderate cases, and 6 severe cases of hyponatremia. When corrected for elevated plasma glucose levels, no episode of hyponatremia was changed to normal values.

Of the 33 cases of hyponatremia on preoperative evaluation, 25 either remained stable in severity, or the sodium deficiency worsened. Preoperative hyponatremia was a statistically significant factor in development of postoperative hyponatremia ($P < .0001$). Sodium abnormalities occurred most often on postoperative day 1. The largest percentage of newly identified episodes occurred with recovery room laboratory tests. Percentage of cases that followed a previously abnormal value increased with each postoperative day. Of the 22 cases of moderate hyponatremia, 16 had a prior abnormal value, and 6 presented with this level of deficiency. All 6 cases of severe hyponatremia had a prior hyponatremic abnormality identified.

Hyponatremia more often occurred in women ($P < .048$). Older patients were also more susceptible ($P < .0001$). Similarly, patients with hyponatremia were lower weight ($P < .009$). However, when weight was adjusted for height (as per body mass index), there was no between-groups difference in developing hyponatremia ($P = .1$). Overall, patients with postoperative hyponatremia received intraoperative fluids in a larger volume ($P < .04$). Subsequent IV and oral fluid intake was less than in normal patients, so total input for the first 24 hours was not different ($P > .2$). However, patients who became hyponatremic had less output ($P < .004$), leading to an

Table I. Overall Patient Demographics With Characteristics Divided Into Normal and Hyponatremic Subgroups

No. of Procedures	**392**		
Site	253 knees	139 hips	
Sex	**215 women**	**177 men**	
Hyponatremic	95 women	60 men	*P* < .05
Age, y	**70.4 (range, 40-96)**		
Normal vs hyponatremic	68.4 (range, 40-90)	73.7 (range, 48-96)	*P* < .001
Height, in	**67.1 (range, 54-78)**		
Normal vs hyponatremic	67.7 (range, 54-77)	66.1 (range, 57-78)	*P* = .15
Weight, lb	**181.8 (range, 90-315)**		
Normal vs hyponatremic	185.9 (range, 90-315)	175.3 (range, 103-296)	*P* < .009
Body mass index	**28.7 (range, 17.6-45.2)**		
Normal vs hyponatremic	29.0 (range, 17.6-41.9)	28.1 (range, 18-45.2)	*P* = .1

overall larger positive fluid balance the first day after surgery ($P < .013$). This continued on postoperative day 2 as a smaller diuresis volume and a subsequent smaller overall negative fluid balance ($P < .012$) (**Table II**).

Knee arthroplasty patients were more prone to developing postoperative hyponatremia than hip arthroplasty patients were ($P < .04$). This association may be attributable in part to the increased postoperative IV fluid and increased total fluid input for knee compared with hip patients ($P < .002$ and $P < .02$, respectively). Of the knee arthroplasty patients, those who underwent simultaneous bilateral surgery were more likely to develop hyponatremia ($P < .0001$), also possibly because of increased fluid input after surgery ($P < .05$). Normonatremic and hyponatremic hip arthroplasty patients had fewer variations in postoperative fluid status compared with knee arthroplasty patients.

Postoperative hyponatremia was associated with use of some but not all of the previously reported medications evaluated in this study. Forty-two cases of hyponatremia occurred in 83 patients receiving a perioperative thiazide ($P < .02$). Thirty-eight episodes of hyponatremia occurred in 76 patients receiving an ACE inhibitor ($P < .05$). Contrary to previous reports, furosemide, selective serotonin receptor inhibitors (SSRIs), and gabapentin were not associated with postoperative development of a sodium deficiency ($P > .2$ for each).

Patients who developed hyponatremia were more likely to have postoperative nausea after either hip or knee arthroplasty ($P < .01$). Length of hospital stay was similar after hip arthroplasty for both groups (normonatremic, hyponatremic), but hyponatremic patients had a longer stay after knee arthroplasty (2.2 vs 2.7 days, $P < .02$). Mental status changes were infrequent overall and did not differ between patient groups. Twelve patients were discharged before complete resolution of their hyponatremia. Five of the 12 had hyponatremia before surgery. Eleven of the 12 had normalization of sodium levels in the days after discharge, as monitored with outpatient laboratory tests.

There were 3 cases of severe hyponatremia, which required additional hospitalization. One of these patients had resistant hyponatremia, and her electrolyte abnormity required prolonged medical hospitalization and management. Her deficiency reached a nadir of 117 mmol/L, and she had episodes of nausea and confusion before resolution. The other 2 patients, discharged with normal sodium values, later developed hyponatremia symptoms, including malaise, confusion, and weakness, and subsequently required hospital treatment.

Three weeks after surgery, a male patient developed hyponatremia and presented with malaise. He was treated with rehydration and ACE inhibitor discontinuation. Ten days after surgery, a female patient developed severe hyponatremia and became delirious. Her deficiency reached a nadir of 116 mmol/L, and she required fluid resuscitation and 3% hypertonic saline infusion. Her hyponatremia was thought to be caused by the syndrome of inappropriate antidiuretic hormone secretion or by an effect of thiazide or citalopram.

Discussion

Hyponatremia is the most commonly occurring electrolyte abnormality in clinical practice.[3,13] In this elective joint arthroplasty study population, hyponatremia occurred often (40%)

Table II. Perioperative Fluid Input and Output in Milliliters per 24-Hour Shift, With Categories Divided by Surgical Site or by Normal Versus Hyponatremic States

	POD-0 Fluid						POD-1		
	Intraoperative IV Fluid	IV	Oral	Total Input	Output	Overall Balance	Input	Output	Overall Balance
All									
Knee	3037	1820[a]	1047	5904[a]	3026	2878[a]	1784[a]	2419[a]	-633[a]
Hip	2955	1637	1079	5605	3048	2580	1456	1610	-264
All									
Normal	2954	1807	1136	5861	3217	2657	1699	2408	-722
Hyponatremic	3097[a]	1681[a]	931[a]	5710	2738[a]	2971[a]	1765	2195	-414[a]
Knee									
Normal	2945	1860	1150	5956	3231	2725	1760	2555	-793
Hyponatremic	3161[a]	1765	906[a]	5833	2748[a]	3085[a]	1814	2252[a]	-437[a]
Hip									
Normal	2969	1719	1114	5707	3195	2547	1450	1489	-273
Hyponatremic	2924	1448[a]	997	5371	2713	2658	1465	1782	-251

Abbreviations: IV, intravenous; POD, postoperative day.
[a]$P < .05$.

and was associated with nausea and extended hospital stays. Studies have supported the finding that even serum sodium levels typically considered normal or low normal (eg, 133 to 137 mmol/L) are associated with prolonged hospital stays, discharge to facilities, and increased mortality, as much as 7-fold to 60-fold.[14,15] Early identification of small decreases in sodium levels is important in identifying patients at potential risk for developing the severe morbidities associated with postoperative hyponatremia.

A limitation of this study is its population size. A larger, multicenter study would increase study size but might introduce confounding variables. Patients did not undergo daily laboratory monitoring after discharge, and therefore additional episodes of postoperative hyponatremia may have gone undetected.

Although the majority of postoperative episodes of hyponatremia are mild and resolve uneventfully, mortality risk increases with even a mild electrolyte disturbance.[14,16] Patients have died with sodium values as high as 128 mmol/L.[17] Severe hyponatremia has been reported to occur in 3% to 7% of hospitalized patients, with a mortality rate near 45%.[2,6,14,18] Specific to orthopedic patients, mortality is higher in those with hyponatremia, 2.1-fold in mild cases, and 4.6-fold in more severe cases.[16] In addition, hyponatremia has been reported to occur in 5.1% of lower extremity arthroplasty patients, with severe episodes causing complications.[19,20]

Hyponatremia is a particularly challenging perioperative problem because symptoms can be mild or overlooked while the deficiency is rapidly worsening. It is important to realize that mild deficiencies may be a warning sign; they usually precede more severe episodes of hyponatremia. In the present study, 73% of moderate cases and 100% of severe cases had low sodium levels identified before they reached their nadir. Hyponatremia that develops after hospital admission or surgery is associated with treatment-related factors and inadequate or delayed management that allows worsening of the deficiency and exposure to the dangers of hyponatremia.[6] Avoiding worsening hyponatremia is crucial, as mortality rates are as much as 50% higher in patients with even asymptomatic degrees of hyponatremia compared with normonatremic patients.[2,13]

Hyponatremia is multifactorial in origin. One cause is thought to be nonosmotic secretion of vasopressin, also known as antidiuretic hormone (ADH), after the stress of surgery or associated postoperative pain.[13,21] The perioperative stress response can last for 12 hours after minor surgery, or for 4 days after major surgery.[22-24] Hyponatremia is also associated with the acute-phase response, with C-reactive protein and interleukin 6 as examples, after surgery by causing a state of antidiuresis.[21,25] Similarly, in the present study, hyponatremic patients overall had more fluid intake and retained more fluid than their normonatremic counterparts did.

Hip and knee arthroplasty may be enough of a surgical stress to initiate hyponatremia. In this study, knee arthroplasty patients developed hyponatremia more often than hip arthroplasty patients did—possibly as a result of increased stress. Similarly, bilateral knee arthroplasty patients were hyponatremic more often than single arthroplasty patients were. Evaluation of a Medicare total knee arthroplasty population revealed that fluid and electrolyte disorders were among the top 10 reasons for 30-day readmission.[26]

Preoperative hyponatremia, lower body weight, female sex, and older age are associated with development of postoperative hyponatremia. As 50% of body water is in skeletal muscle, smaller patients develop hyponatremia when much less electrolyte-free water is retained.[7,27] Overexpansion of the extracellular fluid volume stimulates excretion of sodium and hypertonic urine.[28] Furthermore, the risk that low body weight poses for development of hyponatremia is magnified in the elderly, and therefore elderly women face a combination of risks.[1,13,29]

There is wide variation in quantity and type of IV fluid and electrolytes infused after surgery.[30-32] Dextrose-containing fluid should be avoided in elderly orthopedic patients, as it is a hypotonic solution.[27,33] There may be dilution of intravascular sodium with hypotonic solutions given intravenously, or an extracellular shift of free water into the vascular system after surgery.[20] In particular, lower extremity arthroplasties performed with regional anesthesia traditionally are given more IV fluid (albeit probably not necessary) to counteract the effects of sympathetic blockade.[34]

Use of diuretics, particularly thiazide, has been identified as the most common cause of hyponatremia—affecting up to 14% of all users and up to a third of elderly hospitalized patients.[2,12,35,36] Duration of thiazide use until development of symptomatic hyponatremia ranged from 1 day to 12 years.[3] In addition, ACE inhibitors increase ADH levels in the perioperative period and increase sodium excretion in the urine.[37] According to a case report on a total knee arthroplasty patient taking these medications, electrolytes were not monitored until seizures prompted an evaluation that revealed severe hyponatremia.[37]

Although most of the patients in the present study were not hyponatremic while taking thiazides or ACE inhibitors before their surgery, these medications combined with the stress of surgery or fluid shifts may have predisposed them to develop a sodium abnormality. SSRIs and loop diuretics have also been associated with hyponatremia, but neither was a factor in this study.[2,12] For surgical patients, routine medications such as antibiotics, nonsteroidal anti-inflammatory drugs, and opioids have been associated with development of hyponatremia, as these medications enhance ADH release.[25]

In this study, normal or near normal sodium levels on day of discharge did not preclude development of severe hyponatremia weeks later. Awareness of the prolonged effects of surgical stress on fluid balance through ADH and of the continued risks associated with medications taken after surgery is important in understanding that severe hyponatremia can also develop after hospital discharge.

Conclusion

Although common postoperative sequelae of arthroplasties are most often benign, it is imperative to be aware that hyponatre-

mia may be an underlying cause. This electrolyte abnormality may masquerade as nausea, fatigue, mental status changes, and gait disturbances but can rapidly worsen to cause more serious complications. Preoperative risk factors for developing hyponatremia include female sex, older age, lower body weight, and preoperative sodium deficiency. Hypotonic perioperative IV solutions should be avoided, and perioperative fluid balance should be carefully monitored to avoid dilutional effects, especially in more stressful surgical procedures, which also increase risk. Thiazides and ACE inhibitors should be discontinued when hyponatremia is identified. Awareness of the incidence and risk factors of hyponatremia is crucial for timely identification and prompt treatment.

Dr. Sah is Medical Co-Director, Dearborn–Sah Institute for Joint Restoration, Center for Joint Replacement, Fremont, California.

Address correspondence to: Alexander P. Sah, MD, Dearborn–Sah Institute for Joint Restoration, Center for Joint Replacement, 2000 Mowry Ave, Fremont, CA 94538 (tel, 510-818-7200; fax, 510-793-4318; e-mail, asah@dearbornsah.com).

Am J Orthop. 2014;43(4):E69-E73.

References

1. Adrogué HJ, Madias NE. Hyponatremia. *N Engl J Med*. 2000;342(21):1581-1589.
2. Clayton JA, Le Jeune IR, Hall IP. Severe hyponatraemia in medical inpatients: aetiology, assessment and outcome. *QJM*. 2006;99(8):505-511.
3. Chow KM, Szeto CC, Wong TY, Leung CB, Li PK. Risk factors for thiazide-induced hyponatraemia. *QJM*. 2003;96(12):911-917.
4. Lobo DN. Fluid, electrolytes, and nutrition: physiological and clinical aspects. *Proc Nutr Soc*. 2004;63(3):453-466.
5. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology*. 2008;109(4):723-740.
6. Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. *Nephrol Dial Transplant*. 2006;21(1):70-76.
7. Lane N, Allen K. Hyponatraemia after orthopaedic surgery. *BMJ*. 1999;318(7195):1363-1364.
8. Renneboog B, Musch W, Vandemergel X, Manto MU, Decaux G. Mild chronic hyponatremia is associated with falls, unsteadiness, and attention deficits. *Am J Med*. 2006;119(1):71.
9. Dilorio TM, Sharkey PF, Hewitt AM, Parvizi J. Antiemesis after total joint arthroplasty: does a single preoperative dose of aprepitant reduce nausea and vomiting? *Clin Orthop*. 2010;468(9):2405-2409.
10. Grattidge P. Nausea and vomiting after major arthroplasty with spinal anaesthesia including morphine: a randomised trial of subhypnotic propofol infusion as prophylaxis. *Acta Anaesthesiol Scand*. 1998;42(1):124-127.
11. Miyagawa Y, Ejiri M, Kuzuya T, Osada T, Ishiguro N, Yamada K. Methylprednisolone reduces postoperative nausea in total knee and hip arthroplasty. *J Clin Pharm Ther*. 2010;35(6):679-684.
12. Liamis G, Milionis H, Elisaf M. A review of drug-induced hyponatremia. *Am J Kidney Dis*. 2008;52(1):144-153.
13. Upadhyay A, Jaber BL, Madias NE. Incidence and prevalence of hyponatremia. *Am J Med*. 2006;119(7 suppl 1):S30-S35.
14. Wald R, Jaber BL, Price LL, Upadhyay A, Madias NE. Impact of hospital-associated hyponatremia on selected outcomes. *Arch Intern Med*. 2010;170(3):294-302.
15. Tierney WM, Martin DK, Greenlee MC, Zerbe RL, McDonald CJ. The prognosis of hyponatremia at hospital admission. *J Gen Intern Med*. 1986;1(6):380-385.
16. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med*. 2009;122(9):857-865.
17. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med*. 1992;117(11):891-897.
18. Hawkins RC. Age and gender as risk factors for hyponatremia and hypernatremia. *Clin Chim Acta*. 2003;337(1-2):169-172.
19. Malin JW, Kolstad K, Hozack WJ, Rothman RH. Thiazide-induced hyponatremia in postoperative total joint replacement patient. *Orthopedics*. 1997;20(8):681-683.
20. Gluck GS, Lachiewicz PF. Symptomatic hyponatremia in patients undergoing total hip and knee arthroplasty. A report of three cases. *J Bone Joint Surg Am*. 2008;90(3):634-636.
21. Swart RM, Hoorn EJ, Betjes MG, Zietse R. Hyponatremia and inflammation: the emerging role of interleukin-6 in osmoregulation. *Nephron Physiol*. 2011;118(2):45-51.
22. Gosling P. Salt of the earth or a drop in the ocean? A pathophysiological approach to fluid resuscitation. *Emerg Med J*. 2003;20(4):306-315.
23. Philbin DM, Emerson CW, Coggins CH, Moss JM, Slater E, Schneider RC. Renin catecholamine and vasopressin response to stress of anesthesia and surgery? *Anesthesiology*. 1979;51(3):S122.
24. Brazel PW, McPhee IB. Inappropriate secretion of antidiuretic hormone in postoperative scoliosis patients: the role of fluid management. *Spine*. 1996;21(6):724-727.
25. Beukhof CM, Hoorn EJ, Lindemans J, Zietse R. Novel risk factors for hospital-acquired hyponatraemia: a matched case–control study. *Clin Endocrinol*. 2007;66(3):367-372.
26. Vorhies JS, Wang Y, Herndon JH, Maloney WJ, Huddleston JI. Decreased length of stay after TKA is not associated with increased readmission rates in a national Medicare sample. *Clin Orthop*. 2012;470(1):166-171.
27. Shafiee MAS, Bohn D, Hoorn EJ, Halperin ML. How to select optimal maintenance intravenous fluid therapy. *QJM*. 2003;96(8):601-610.
28. Steele A, Gowrishankar M, Abrahamson S, Mazer D, Feldman RD, Halperin ML. Postoperative hyponatremia despite near-isotonic saline infusion: a phenomenon of desalination. *Ann Intern Med*. 1997;126(1):20-25.
29. Wilkinson TJ, Begg EJ, Winter AC, Sainsbury R. Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol*. 1999;47(2):211-217.
30. Stoneham MD, Hill EL. Variability in post-operative fluid and electrolyte prescription. *Br J Clin Pract*. 1997;51(2):82-84.
31. Walsh SR, Walsh CJ. Intravenous fluid–associated morbidity in postoperative patients. *Ann R Coll Surg Engl*. 2005;87(2):126-130.
32. Callewart CC, Minchew JT, Kanim LE, et al. Hyponatremia and syndrome of inappropriate antidiuretic hormone secretion in adult spinal surgery. *Spine*. 1994;19(15):1674-1679.
33. Tambe AA, Hill R, Livesley PJ. Post-operative hyponatraemia in orthopaedic injury. *Injury*. 2003;34(4):253-255.
34. Hübner M, Schäfer M, Demartines N, et al; Zurich Fast Track Study Group. Impact of restrictive intravenous fluid replacement and combined epidural analgesia on perioperative volume balance and renal function within a Fast Track program. *J Surg Res*. 2012;173(1):68-74.
35. Byatt C, Millard PH, Levin GE. Diuretics and electrolyte disturbances in 1000 consecutive geriatric admissions. *J R Soc Med*. 1990;83(11):704-708.
36. Clayton JA, Rodgers S, Blakey J, Avery A, Hall IP. Thiazide diuretic prescription and electrolyte abnormalities in primary care. *Br J Clin Pharmacol*. 2006;61(1):87-95.
37. Chakithandy S, Evans R, Vyakarnam P. Acute severe hyponatraemia and seizures associated with postoperative enalapril administration. *Anaesth Intensive Care*. 2009;37(4):673-674.