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Effectiveness of Pamidronate Usage in RCU Admitted Patient in Reducing Mortality Rate

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Keywords: *eGFR = estimated glomerular,; CI = confidence interval; CKD = chronic kidney disease; CTx = C-telopeptide; filtration rate; NTx = N-telopeptide; PMV = prolonged mechanical ventilation; RCU = respiratory care unit; CCI = chronic critical illness ICU = intensive care unit.*

ABSTRACT

Aim: We've seen it—evidence that using intravenous (or IV) pamidronate to treat serious chronic critical illnesses can turn back the tide on bone resorption. This study? Well, it scrutinizes how pamidronate impacts clinical outcomes in folks grappling with these longstanding, severe health issues.

Methods: Look at it this way, from May 2016 stretching over the course of more than four long years till October 2020, a comprehensive study tracking retrospectively a total of 108 patients was carried out meticulously in two different locales. The intense critical care units of Iraq's highly reputed Burn Specialty Teaching Hospital and Ghazi AL Hariri Teaching Hospital for Special Surgery were those locations. Now we had identified Chronic Critical Illness (CCI) afflicted patients who were chosen to be given IV bisphosphonate within the range between thirty to ninety milligrams or alternatively not administered at all but just monitored otherwise (the count goes about hundred-eighteen). It was interesting that there seemed no difference as such whether their renal function was found normal or sorta impaired uniformly across both cohorts of patients under analysis. So why were they given Bisphosphonate? Well pretty straight forward - combat hypercalcemia and hypercalciuria.

Results: evaluation of serum calcium concentration and GFR, with a marginally significant relationship for RCU deadliness (P value = 0.0911) and a correlation to reduced mortality that remained after a year (P = 0.0132). A week after pamidronate was applied, we saw a major drop in creatinine levels (the P value stands at 0.0025). Interestingly though, no noticeable shift was found another week on from that already significant reduction. Over in the RCU where nurses were keeping an eagle eye on things, the level of s.albumin belonging to patients assigned to pamidronate showed more increase (from 2.49 up to 3.23 g/dl) than did those who didn't go under medication¬–it only managed a mild raise from 2.43 and settled at just about 2.64 g/dl,. And get this; there's still something else interesting with an infinitesimal P value of .0007! Moreover, sprinkling some pamidronate into the mix significantly cut back occurrences of hypoglycemia (down from a rate of 0.12 down to practically negligible, sitting slimmer than ever at only around about roughly approximately quasi-approximate low-levels like maybe perhaps circling somewhere roundabouts pretty much virtually essentially almost near-as-makes-no-difference give-or-take nigh-on nearly barely scraping topside of survived-above-the baseline density sequence normal rather scantiness mere hardly anything notably basic purely essential plain simple suitably fundamental largely adequate substantially

rarely seldom further lesser fewer less decreased limitation declining regression descent fall-off fade-out shrinkage diminution let-up easing slowing-down falloff decrement depletion weakening slackening receding abatement-amnestic-rates soaring as they do quite towards extremely low figure almost nothing point-zero-nine-times-not-in-a-hundredths - impressive isn't it? Absolutely below moon-clear or sundown-obvious when you step them out neat side by side against RCU regulars absolutely done-without any such medical treatment whose internal tempest may well be lying dormant.

Conclusion: Pamidronate therapy is linked to lower mortality, a decreased incidence of hypoglycemia, greater albumin levels, and no change in renal function in the CCI population.

Introduction

There's a certain type of patients with stubborn diseases, who either pass away or fail to recover promptly enough for transferal to the ICU. These folks often need invasive breathing assistance and are lumped into what we call critical chronic illness (CCI). Habitual residency in an intensive care unit can lead up to organ failure and kick off serious financial disasters. Even under optimum medical supervision, some patients still don’t manage good outcomes. A meager 30–53% among them managed without lung-assisting devices; mind you, among these self-breathings survivors, death claimed another 20–40%. Devastatingly enough, on a yearly scale it even reached staggering numbers between 48-68% (1, 2). Moreover, individuals who survive will experience several comorbidities and insufficient medical attention. (3). Increased inflammatory indicators brought on by cytokines and immunosuppression, as well as multiorgan dysfunction including PMV, cachexia, and neuroendocrine dysfunction, are indicative of metabolic instability in patients with CCI. The symptoms include wound infection, hyperglycemia, resorption stress, myopathy, polyneuropathy, and cognition impairment (4-6). Se We should definitely acknowledge this - severe diseases frequently link with, well, high bone turnover. Normally in a healthy population, you've got the formation of bone by these cells called osteoblasts and the degradation of bone by another group known as osteoclasts working to patch up bones tissues-they're like best friends indeed! However, there are things that can throw off their friendship. Too little sunshine (sunbathing has its merits), plain old poor nourishment-oh and let's not forget some nasty organ diseases too- they all could lead to less vitamin D than needed. Here is where it gets more complicated; if your body goes into secondary hyperparathyroidism mode, then damn! Your process of bone resorption just took a turn for the worse. On account of the aforementioned unrest, we believe that severe illnesses have the ability to interfere with this linking and encourage osteoclast absorption. This interference might ramp up osteoclast activity alongside bone resorption (9), leading also to a push for more osteoclast genesis due to elevated cytokines such as TNF and IL6, IL1 (10). Consider this! Extended periods of bed rest can often trigger bone resorption in patients grappling with spinal cord injuries (11). Alternatively, an absolute or relative increase in bone re-absorption over bone production may be the result due to distinct endocrine disorders. These might include conditions such as hypogonadism, decreased levels of insulin-like growth factor and hypercortisolism(12). Now for RCU patients, restoring this lost bone density proves arduous. The sheer challenge results in pathological fractures and total osteoporosis falling headlong into their paths (13).

Bisphosphonates can't halt the speeding up of bone breakdown but they can lend a helping hand (14, 15).

Take patients suffering from acute spinal cord injury. It has been shown that a single dosage of prepamidronate, at 90-mg, can cause significant reductions in NTx and hypercalciuria (11).

While it's clear that bone markers are diminished by intravenous bisphosphonates, we're uncertain if the reaction to bisphosphonates tends to improve in these patients. We hypothesized

a boost in muscle strength might relate back to bettered bone and mineral metabolism - could this decrease their need for respirators or even have sweeping effects on the immune system? Supposing pamidronate exerts indirect influence, such an outcome isn't too remote. Bear in mind, CCI patients undergo complex molecular alterations alongside noteworthy physiological shifts. Rewritten Text: "Let's really look into the intriguing influences of pamidronate. Now consider its effects on the death rates and requirement for respirator assistance amongst chronic kidney injury folks— also known as CCI patients. Then, think about how this medication might interact with their kidney function. And finally, to add a bit more intrigue to our investigation, we dove deep into relevant biochemical markers—and statistically diced them apart—to form theories about why pamidronate might affect these patients' health outcomes in the ways that it does.

METHODS :

From May 2016 to October 2020, a study was conducted that included patients who were hemodynamically stable and those considered critical (namely, those with CCI) requiring tracheotomies and PMV. This research took place in the intensive care units of Iraq's Burn Speciality Teaching Hospital as well as the Critical Care Center at Ghazi AL Hariri teaching hospital for special surgeries. The Treatment teams includes not only Intensive Care but also pulmonary specialists whenever patients are admitted to the RCU. And it goes without saying, nurses don't function alone; they join forces with physicians, endocrinologists along rare collaborations with respiratory therapists followed by some exceptional coupling with physiotherapists. Our primary goal, when working with patients lodged in the intensive care unit, is to get them off of the ventilator. There's plenty of strategies - an odd mixture ranging from conservative to outright unconventional- that have been drummed up targeting this area to fine-tune metabolic treatments. Regularly, tests are run on patients using a multitude of metabolic benchmarks in conjunction with other criteria. If blood test results point to hypercalciuria, or too much calcium in urine; hypercalcemia, unusually high levels of calcium in your blood; or bone resorption is occurring that's obvious—a process where your bones break down and release minerals into the bloodstream— then intravenous pamidronate often comes up as a treatment preference.

Study design

So, here's what happened. Each and every patient who found their way to the hospital - from May 2016 all the way through to October 2020 - was assessed by this one specific endocrinologist, a certain RCS. The same person hoovered up data using electronic patient records specially designed for hospitals and reviews of old charts that were looked back upon retrospectively. And then? Well information on drugs, people (like how old they are and where they're living) as well as biochemists' insights got zapped straight into an electronic format so it could reside in our trusty hospital data warehouse. Let's dive into the specifics. We're talking about anonymized patient details, all of 'em. The gamut spans from their demographics to time spent on mechanical ventilation, even their usage of pamidronate and pre-existing kidney disease. Nutritional assistance received by each one is also noted down alongside biochemistry data with steps on procuring the RCU info - got it? Now let’s get technical for a sec here – we need to comb through some calculations about protein energy levels for every patient. And if you're wondering how that's done- well, patients who had a body mass index or BMI equaling or exceeding 25 kg/m2 used an equation (ABW – ICC) × 0.4 + ICC to measure both actual body weight (ABW) as well as ideal body weight (IBW). 148 patients suffering from chronic critical illness were our choice for this study. Out of these, pramidronate- an IV injected drug was administered with doses ranging between 30 to 90 mg, in the case of only 30 folk. The remaining lot which accounted for a total count up to about one hundred and eighteen had given it a miss. Parameters related to chronic kidney disease (CKD)- along with both categories showcasing

normal functioning kidneys- have been calculated meticulously by us.

By undertaking some alternations in dietary habits, we could successfully determine what's referred as 'eGFR'; an acronym that stands for the estimated glomerular filtration rate.

For pamidronate treatment concerning renal illness, a range of criteria has been established. Let's discuss these in detail shall we? Firstly and rather importantly if you ask me, urine NTx should be greater than or equal to 70 nmol bone collagen equivalents (BCE) per mmol creatinine—such was the case with 15 patients. As well as that, serum NTx should be more than or just exactly equal to 40 nM EBC/L—in three cases only this status quo occurred. A third interesting fact is the quantity of urinary calcium over 24 hours - it must exceed or at least meet up with a cool total of whopping 250 mg which happened much often enough across eleven cases! And lastly on our list today folks ionized calcium levels are required above the satisfactory reading of >1.29 mmol/L—which there was one such odd incident.

The dosage here is peculiar indeed; either they received from their friendly neighborhood healthcare worker merely around thirty-to-sixty milligrams bathed atop six enjoyable immersive hours -or- lo-and-behold an extravagant menstrual dose acquired gallantly absorbing attached commendable ninety-minute infusion spanning four long dedicated hours! An endocrinologist keenly evaluates each patient’s unique equation singularlinear-fashion keeping a close eye especially on those carrying around slightly leaner body weight dimensions lurking inside.

Our small part in pamidronate trials unraveled quite bizarre phenomena I say; not one amnesiac mind-numbing statistic but two treatments were given during hospital stay enjoyed by no less than exuberant trio full lucky selected experimental participants whereas sole single doses served happily therapeutic purposes for higher number yielding crowning jewel grand sum of twenty-seven thus indoors.

Different dosages are used, yeah. Turns out, 26 bright patients (making up a whopping 87%) got their veins juiced up with 90 mg of pamidronate intravenous glory juice. One lone-ranger patient (that's around 3%) scored the lower end dose of just merely60mg and barely three daring individuals(making up solid10% folks) scored a bare minimum30 mg serving. Say there’s an alarming rise in those bone markers—tangibly scary beasts requiring ‘another round’ (we're talking dirty deed here- that'd mean another dosage between anything from your standard ol' thirty to ninety milligrams-heavyweight medicine), likely coming at ya two weeks after you've been bashed by that initial hit! Eagerness aside, our steadfast Pamidronate injection faces delays while patients battle feverish conditions. Practically every patient was given a healthy mix of calcium carbonate (1000–1500 mg), basic calcium, ergocalciferol (2000 IU/day) and calcitriol (0.25 mcg/day). But this wasn't the case if contraindications like hyperphosphatemia, an excess of calcium, hypercalciuria or kidney failure existed. The dosage adjustments were made to maintain 25-hydroxyvitamin D at a level that is equal to or above 30 ng/mL.

Statistical analysis

The geometric form Mean (Geo SD) is used to present laboratory values, and patient demographic characteristics were are displayed, on average (SD). To assess changes in each variable between the groups that received and did not receive pamidronate therapy from the time of admission to the RCU, the ANOVA test was employed. The variables included the treatment group and the laboratory variable, which served as the explanatory and dependent variables, respectively. Additionally, the relationship between time and treatment is addressed.

To scrutinise and contrast the time-event curves among patients administered with pamidronate vs. those who were not, we used a log-rank test; this allowed us to execute Kaplan-Meier tests on the cohort. Presently, a fresh comparative study was conducted focusing specifically on 13 days following each patient's admission into an intensive care unit (20). It is of note that whichever treatment protocol was issued to the patient at Landmark institution determined whether or not

they received Pamidronate. At Landmark there is no administration of Pamidronate; thus folks previously treated with it were categorised as non-users in our records: Those who hadn't undergone Pamidronate therapy were excluded from our observation during this timespan. And so commenced the period of administering treatment with Pamidronate".

RESULTS

We're talking about a patient who, when admitted, was at the median age of 68 years—that's between a mind-boggling range from youthful 24 right up to impressive old age of 95. Now get this—on admission, they also tipped the scales at an average weight of 74 kilos and stood with their head held high at around—at average—you guessed it—65 inches. Mind you, that's no layman height; we've got standard deviations in there too! The fella had a BMI—if calculations are precise—to be noted down as approximately 27.6 kg/m^2. And guess what? They were committed to the long hall—it wasn't just one or two days but on average a whole-long winded haul of fifty-five exhausting days with ranges flitting from quick-stay eight to staggering four hundred and six-day stays! Of course not all leisurely hospital bed vacation—the stay included intensive RCU time averaged out across many cases somewhere near twenty-seven days—incredibly varying drastically anywhere between short visits for three-days flat compared with longer encounters dealing up-to an entirety massive stint of almost half-a-year i.e.,160 solid recovery demanding days! When the patients finally left the intensive care ward, their respiratory status fell into three categories. Firstly, there were those who were still breathing and alive (78 patients or 53%). Secondly, some required ventilation assistance (48 in number which is around 32%) while sadly for others - about fifteen percent or twenty-two individuals had lost their lives. Fast forward to a year from RCU departure date; death was recorded for eighty beings – equivalent to over half of them. Additionally, hospital care claimed another nineteen percent equating to slightly above twenty-eight souls during this span. Basic data regarding biochemical parameters? Refer Table-1 that snips both pieces of those thirty pamidronate beneficiaries snug amidst one-hundred eighteen non-recipients.

Patients receiving pamidronate had a considerably lower death rate (0.0%) in RCU compared to patients not receiving treatment (22,19%) (P = 0.0077). After a year, the group that received pamidronate experienced mortality that was similar but considerably lower (7,20%) than the group that did not get pamidronate (66,56%) (P = 0.0004). The connection between mortality reduction and baseline creatinine, eGFR, and s. calcium levels did not change when group differences were taken into consideration.

After a year, the result has become significant (P = .0132), but inconsequential regarding death in the RCU (P = 0.0911). According to a Cox proportional hazard model drawn from a 13-days analysis in RCU, patients who were on pamidronate have appeared to consume more. But alas! This discrepancy holds no statistical significance i.e., hazard ratio stands at comfortable 1.93; confidence level is strong at 95% and straddles from twilight eight p.m till late afternoon four-thirty with P value hovering just above one (P=0.1088). Sagacity of Kaplan-Meier curve for pamidronate members discloses higher odds of ventilator use liberation as depicted in Fig.1A alongside tracheostomy series manifestation etched out vividly by Fig. B. In our retrospective analysis of 89 patients, it was found that eight (67%) out of twelve individuals who received Pamidronate and had been discharged were on respirators. Interestingly enough, this is in comparison to the twenty-four folks (31%) outta' the seventy-seven who didn't receive any treatment. About a quarter of those pampered with Pamidronate managed to get themselves released from their health-related complications within nine sweet days - give or take three to twenty-three days if you want specifics (95% CI). On the other hand, we've got some stragglers among those that weren't given any aid; they walked away looming between four and a long twenty-four days post-treatment(25%). That's an average wait time looking around eleven

sunsets longer than their treated counterparts(log-rank P=.0971), as per data crunched through Kaplan-Meier analyses.

Table 1 Selected Baseline Biochemical Information for Research Participants Admitted to RCU

	Overall N = 148	Pamidronate n = 30	Non Pamidronate n = 118	P value
Albumin (3.5-4.9 g/dL) Median [Min-Max] for GeoMean (GeoSD)	147 2.44 (1.24) 2.40 [1.20-3.90]	29 2.49 (1.24) 2.70 [1.50-3.20]	118 2.43 (1.25) 2.40 [1.20-3.90]	.5828
Calcium [mg/dL] (8.5–11.0) Medium (Min-Max) GeoMean (GeoSD)	147 8.47 (1.09) 8.50 [7.10-10.10]	29 8.66 (1.10) 8.60 [7.10-10.10]	118 8.42 (1.08) 8.40 [7.20-10.10]	.1054
Creatinine mg/dL (0.7-1.4) Geomean (GeoSD) Median [Min-Max]	148 0.95 (2.24) 0.80 [0.10-8.80]	30 0.67 (2.30) 0.60 [0.10-4.90]	118 1.03 (2.18) 0.90 [0.20-8.80]	.009
GFR mL/min/1.73 m2 Geomean (GeoSD) Median [Min-Max]	148 62.94 (2.26) 60 [8.94-458.27]	30 81.65 (2.37) 60 [13.31-458.27]	118 58.91 (2.21) 60 [8.94-443.70]	.0502
Magnesium mg/dL (1.5-2.5) GeoMean (GeoSD) Median [Min-Max]	147 2.00 (1.16) 2 [1.10-2.90]	29 2.02 (1.15) 2 [1.60-2.90]	118 1.99 (1.16) 2 [1.10-2.90]	.7129
NTx serum nmol BCE/L (<40) GeoMean (GeoSD) Median [Min-Max]	4 40.00 (1.00) 40 [40-40]	3 40.00 (1.00) 40 [40-40]	1 40.00 (NE) 40 [40-40]	Not estimable
NTx urine nmol BCE/mmol creatinine (3.0-51.0) GeoMean (GeoSD) Median [Min-Max]	10 145.90 (2.21) 122.50 [55-581]	7 154.58 (2.04) 151 [73-581]	3 127.50 (3.06) 83 [55-454]	.7467
Phosphorus mg/dL (2.4-4.7) GeoMean (GeoSD) Median [Min-Max]	147 3.38 (1.31) 3.40 [1.60-7.40]	29 3.24 (1.19) 3.1 [2.3-4.8]	118 3.42 (1.34) 3.4 [1.6-7.4]	.3318
PTH intact pg/mL (16-87) GeoMean (GeoSD) Median [Min-Max]	7 104.20(2.33) 86 [32-376]	2 48.33 (1.79) 52.5 [32-73]	5 141.69 (2.14) 150 [54-376]	.1384
1,25-Dihydroxyvitamin D pg/mL (1.2499-67) GeoMean (GeoSD) Median [Min-Max]	129 19.19 (2.08) 18 [8-79]	25 22.34 (2.21) 28 [8-79]	104 18.51 (2.04) 17 [8-79]	.249
25-Hydroxyvitamin D ng/mL (≥30) GeoMean (GeoSD) Median [Min-Max]	141 13.84 (1.78) 14.6 [4-60.4]	29 15.65 (1.81) 17.3 [4-36.20]	112 13.40 (1.77) 14.45 [4-60.4]	.1964

Abbreviations: BCE = collagen equivalent; GeoMean = geometric mean; GeoSD = geometric standard deviation; GFR = glomerular filtration rate; NTx = N-telopeptide; PTH = parathyroid hormone; RCU = Respiratory Care Universityi

The groups not receiving pamidronate and the groups receiving pamidronate represented all stages of CKD. Phamidrate group (0-2, 26 [87%]; stage 3, 1 [3%]; 4, 2 [7%]; 5, including patients receiving renal replacement therapy [RRT], 1 [3%]) and non-recipients (grades 0-2, age 74 [63%]; grade 3, age 23 [20%]; grade 4, age 11 [9%]; grade 5, grade 9 [9%] 8%]) had their CKD status determined. At the time of RCU confirmation, pamidronate recipients had a brutal pattern (SD) creatinine level of 0.67 (2.30) mg/dL compared with 1.03 (2.18) mg/dL in nonrecipients (P = 0.009). Pamidronate collectors' eGFR was 81.65 (2.37) mL/min/1.73 m2 at the time of RCU admission, while non-receivers' eGFR was 58.91 (2.21) mL/min/1.73 m2 (P =.0502). The change in the eGFR from RCU affirmation to release increased for pamidronate users (81.65 to 87.96 mL/min/1.73 m2) and dropped for no recipients (58.91 to 57.64 mL/min/1.73 m2), all without exceeding centrality (P =.3165). Days after pamidronate administration (P =.0180), creatinine levels were considerably lower 7 days (P =.0025) and 9 days (P =.0025) in the pamidronate subgroup. At 14 days, there was no discernible change from baseline (Table 2). The variation in average eGFR between. For pamidronate, the length of stay from admission to discharge from the RCU has grown. declines in non-receivers (58.91 to 57.64 mL/min/1.73 m2) and receivers (81.65 to 87.96 mL/min/1.73 m2) that reached statistical significance (P =.3165).

Nutrition and albumin :

The total cohort's mean (SD) required days to reach nutritional energy objectives (20–25 kcal/kg/day) was 0 (range 0–13 days); this equates to 0.9 (2.3) days. Most of the patients in the research were fed using enteral nutrition. During the second assessment of the Pamidronate status, the protein quantity (1.2 [range, 0 to 2.2] g/kg/day against 1.2 [range 0-2.4] g/kg/day days; P = 0.425) and energy amount (26.1) [range, 0 to 34.3] kcal/kg/day versus 24.7 [range, 0 to 40.7] kcal/kg/day days; P = 0.2356) were found in the Pamidronate and non-pamidronate groups. The RCU's The discharge time was similar.From the emergency room to discharge, patients treated with pamidronate showed a substantially higher average serum albumin level improvement (albumin rise from 2.49 to 3.23 g/dL) compared to those who did not receive treatment (albumin increase of 2.43). when the duration of hospital stay in the UCI and the albumin level upon admission were taken into account (P = 0,0007) at 2.64 g/dl (Table 3). From within Although there was a higher likelihood of ventilator activation across the entire group, they managed to reach an albumin level of 2.5 g/dl (74.95%).45.64%) of non-exemptors (P 0.0001). The average duration for released participants to reach a 2.5 g/dL albumin level was 7.14 days, compared to 19.99 days for liberators.

blood sugar regulation

When admitted, 48 patients (32%) had hemoglobin A1c values of 6.5% (47.5 mmol/mol) or had a history of diabetic mellitus (DM). 85 (or 57%) of them Individuals in the group had to stand outside the RCU to give insulin after receiving a diabetes diagnosis. Glargine and Unbiased were among the insulins used. Hagedorn protamine, lispro, either alone or in combination, and/or regular offence Hagedorn protamine, lispro, either alone or in combination, and/or regular offence (21) Measuring glycemic changeability and mean blood glucose at RCU confirmation and release were compared between receivers of pamidronate and those who did not, but no discernible variations were detected (Table 4). Patients who died within the RCU had a rate of 0.19, while patients who did not die had a rate of 0.10 (P.0001). The rate of hypoglycemia was largely associated with RCU mortality. Additionally, there was a significant correlation found between the rate of hypoglycemia and 1-year mortality (P.0001). The rate of hypoglycemia was 0.09 for patients who did not die within a year, and 0.14 for those who did. Individuals who went

through three or more hypoglycemia episodes while in the RCU were much more likely to relapse a year later than those who did not (P =.0218). Pamidronate recipients had the same probability of passing away in the RCU even after adjusting for the quantity of hypoglycemia episodes.

They were considerably less likely to expire after a year (P=.0018) as non-recipients (P =.0773).

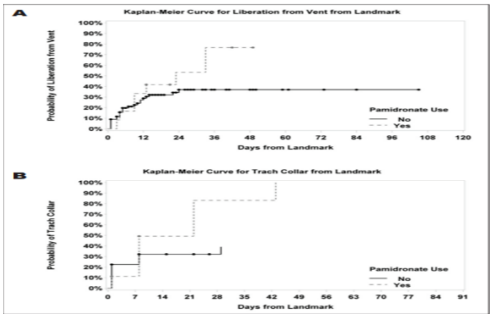

Fig. 1. Kaplan-Meier curves showing the likelihood of tracheostomy collar (B) and ventilator liberation (A) over time in the respiratory care unit for both pamidronate receivers and non-receivers.

Table 2 Creatinine Levels Prior to and Following the Administration of Pamidronate

GeoWSD = 1.17 days before administration	Creatinine (mg/dL) GeoMean (GeoBSD)	GeoWSD = 1.17	Creatinine (mg/dL) GeoMean (GeoBSD)	GeoWSD = 1.17 day after administration	Creatinine (mg/dL) GeoMean (GeoBSD)
14	0.44 (1.45)	Pamidronate administered	0.57 (2.04)	1	0.66 (1.86)
13	0.48 (1.53)			2	0.64 (1.82)
12	0.54 (2.37)			3	0.62 (1.91)
11	0.67 (2.65)			4	0.57 (1.91)
10	0.60 (1.89)			5	0.52 (2.26)
9	0.67 (2.57)			6	0.74 (2.51)
8	0.77 (2.32)			7	0.41 (1.39)
7	0.69 (2.23)			8	0.63 (2.54)
6	0.84 (2.16)			9	0.44 (1.66)
5	0.57 (1.59)			10	0.67 (2.69)
4	0.84 (2.42)			11	0.65 (1.97)
3	0.61 (1.67)			12	0.55 (2.24)
2	0.58 (2.29)			13	0.62 (2.40)
1	0.77 (2.17)			14	0.54 (2.02)

DISCUSSION

Even with technological advancements in the care of critically ill patients, CCI is linked to a high rate of morbidity and death. We postulated that by enhancing certain facets of the pathophysiology of critical care illnesses, overall outcomes might be enhanced. For instance, hyperglycemia brought on by stress is a prevalent characteristic of the CCI subtype. Our team recently found that outcomes in CCI cohorts are correlated with improvements in glycemic control measures (21). Silent but critical, severe disease-related bone loss associated with CCI may be treatable. Our study is noteworthy because it offers the first evidence linking intravenous pamidronate administration to improved mortality outcomes in hospitalized patients with CCI, despite our prior reports of increased bone resorption in CCI (8) and the use of intravenous

bisphosphonates to reduce resorption (14, 15). These relationships persisted even after taking into consideration variations in the groups' baseline renal function and serum calcium levels, especially when it came to one-year mortality.

Table 3 Comparing Selected Biochemical Values for Pamidronate Receivers and No Receivers at RCU Admission and Discharge

	Pamidronate n = 30		Change from admission P value	Non-pamidronate n = 118		Change from admission P value	Difference between changes P value
	Admission	Discharge		Admission	Discharge		
Albumin g/dL (3.5-4.9) GeoMean [GeoSD] Median [Min-Max]	29 2.49 (1.24) 2.70 [1.50-3.20]	23 3.23 (1.24) 3.30 [1.90-4.40]	<.0001	118 2.43 (1.25) 2.40 [1.20-3.90]	116 2.64 (1.29) 2.70 [1.20-4.20]	<.0001	.0007 .0007a
Calcium mg/dL (8.5-11.0) GeoMean [GeoSD] Median [Min-Max]	29 8.66 (1.10) 8.60 [7.10-10.10]	24 9.25 (1.08) 9.20 [8.00-10.30]	.0006	118 8.42 (1.08) 8.40 [7.20-10.10]	116 9.02 (1.10) 9.10 [6.90-11.20]	<.0001	.7403 .7242a
Creatinine mg/dL (0.7-1.4) GeoMean [GeoSD] Median [Min-Max].	30 0.67 (2.30) 0.60 [0.10-4.90]	26 0.58 (1.98) 0.55 [0.20-4.10]	.1895	118 1.03 (2.18) 0.90 [0.20-8.80]	118 1.00 (2.16) 0.90 [0.20-7.10]	.4516	3856 .3821a
eGFR mL/min/1.73 m2 GeoMean [GeoSD] Median [Min-Max]	30 81.65 (2.37) 60 [13.31-458.27]	26 87.96 (2.37) 60 [13.31-458.05]	.4040	118 58.91 (2.21) 60 [8.94-443.70]	118 57.64 (2.14) 60 [9.66-484]	.5615	.3165 .3042a
Phosphorus mg/dL (2.4-4.7) GeoMean [GeoSD] Median [Min-Max].	29 3.24 (1.19) 3.10 [2.30-4.80]	24 3.53 (1.22) 3.60 [2.20-4.60]	.1862	118 3.42 (1.34) 3.40 [1.60-7.40]	117 3.73 (1.28) 3.70 [1.70-6.60]	.0031	9479 .9166a
RCU LOS	23.81 (2.08) 27 [8-160]			30.57 (1.86) 27 [3-137]			

The following are acronyms: LOS stands for length of stay; RCU for respiratory care unit; GeoMean for geometric mean; and eGFR for estimated glomerular filtration rate. adapted to the duration of stay in the RCU.

In a retrospective analysis of 7,830 critically ill patients, Lee and colleagues (22) discovered that, despite the bisphosphonate group's higher comorbidities and older age, in-hospital mortality was lower for patients who received the medication within five years of admission. It is unknown how pamidronate enhances results, although there are a few theories that can be ruled out. Increased bone turnover brought on by systemic inflammation has been connected to a rise in mortality (23). Patients with stage 3 to 4 chronic renal disease who were hospitalized to the RCU and treated with bisphosphonates had a decreased death rate (24). Bisphosphonates have also been demonstrated to lower coronary artery calcification and inflammatory markers in hemodialysis patients (25). Lastly, there is compelling evidence that when given between 14 and 90 days following a hip fracture, zoledronic acid, another intravenous bisphosphonate, increased overall survival in older patients of both sexes (26).

Table 4Blood Glucose (BG) Data for Pamidronate Receivers and Non-Receivers at RCU Admission and Discharge: Evaluation of Mean BG, Glycemic Variability Measures (WSD, range), and Hypoglycemia Rate

	Pamidronate n = 30		Change from admission P value	Non-pamidronate n = 118		Change from admission P value	Difference between changes P value
	Admission	Discharge		Admission	Discharge		
BG (mg/dL)n GeoMean (GeoBSD, GeoWSD)	30 134.29 (1.21, 1.47)	30 125.21 (1.15, 1.27)	.3172	118 132.95 (1.25, 1.25)	118 125.21 (1.21, 1.25)	.047	.9608 .9622
BG within subject SD n GeoMean (GeoSD)	24 18.92 (2.97)	28 20.49 (1.82)	.7045	103 16.78 (2.53)	109 17.81 (2.27)	.6873	.8681 .8677a
BG Range (mg/dL) n GeoMean (GeoSD)	24 30.57 (3.86)	28 46.06 (1.90)	.1312	103 33.78 (2.75)	109 38.47 (2.48)	.349	.3125 .3132a
Hypoglycemia rate (# events/# days in RCU)		101/1125 0.09			430/3556 0.12	.0071	

The following acronyms stand for geometric standard deviation, mean, within-subject geometric standard deviation, and geometric standard deviation between-subjects: GeoBSD, GeoMean, GeoSD, and GeoWSD. Respiratory care unit = RCU. An adapted to the duration of stay in the RCU.

Serum albumin is a nutritional marker, however it may also be a measure of inflammation and liver function, rather than a direct indicator of nutritional health. the degree of inflammation reflected by hypoalbuminemia (27, 28). There is a correlation between the degree of hypoalbuminemia and both higher mortality and reduced respiratory function in critically ill and

injured patients, according to previous study (29, 30). Better treatment outcomes may result from increased serum albumin concentrations in our study's pamidronate users, which may signal a general improvement in pamidronate-mediated inflammation. Not only are our study's results innovative and timely, but they also suggest that pamidronate users had a decreased incidence of hypoglycemia, which may shed light on the mechanisms underpinning our cohort's better outcomes. In critical care units, hypoglycemia has been found to be a predictor of morbidity and death in the past (31), and the CCI cohort has shown comparable correlations (21). Furthermore, there is a significant reduction in short-term mortality after accounting for the prevalence of hypoglycemia. While the long-term (1-year) mortality effect is still significant, the pamidronate effect that we saw in our sample did not reach statistical significance. This data bolsters the idea that the bimodal impact of palidronate may benefit short-term mortality by reducing hypoglycemia; however, other benefits of palidronate may be more significant for long-term mortality. Osteocalcin knockout mice showed reduced beta cell proliferation and enhanced insulin resistance, as reported by Lee et al. (32). On the other hand, osteocalcin treatment raised insulin sensitivity and secretion. Mouse insulin levels Additionally, it raises the synthesis of the adipokine adiponectin, which is an insulin sensitizer. (32). There is an inverse correlation between fasting plasma glucose levels, BMI, and serum osteocalcin levels, according to a recent cross-sectional human investigation (33). (33) Lower levels of undercarboxylated osteocalcin and adiponectin are linked to alendronate treatment of postmenopausal osteoporosis (34), yet even after long-term alendronate treatment, no metabolic phenotype is seen. Remarkably, it was found that low levels of adiponectin were an independent predictor of survival following ICU admission (35). Therefore, it is postulated that pamidronate prevents the synthesis of osteocalcin in a condition of high bone turnover (where serum osteocalcin levels rise as well), which under turn prevents the synthesis of adiponectin. As the standard of care in our population (21), the innovative combination of pamidronate-induced insulin resistance and stringent exogenous insulin administration has the potential to enhance outcomes by lowering the overall incidence of hypoglycemia.

the results of the medical intervention. Insulin resistance, despite its negative connotation, guards against serious sickness by preventing glucose oxidation and, consequently, fostering a protein-sparing effect (36). The aforementioned theory is supported by the improvement in albumin levels shown in our cohort of patients receiving pamidronate. This improvement may be due to improvements in nutritional factors. More investigation is required into the mechanisms by which pamidronate and possibly other bisphosphonates may increase survival in critically ill patients, given the obvious extra-skeletal effects of these drugs (37, 38). Historically, doctors have been reluctant to provide intravenous bisphosphonates in hospital settings due to worries about potential impairment of kidney function. Rather, our research revealed that the administration of pamidronate led to both stability and a minor improvement in renal indices. Despite the fact that zoledronic acid, in particular, has been associated with a higher risk of kidney damage in other populations (such as cancer patients), our results imply that pamidronate is safe for treatment in the CCI population, regardless of renal function. The retrospective and single-center design of our study, the potential for selection bias, and the comparatively small number of patients receiving medication are some of its drawbacks. The absence of pamidronate backwash and baseline readings is another drawback. Since it speeds up bone resorption and heightened inflammatory markers are unlikely to be variables influencing CCI healing and recovery, this confirmation of bias appears questionable. According to our research, pamidronate treatment for osteoporosis resulted in an increase in bone resorption.

CONCLUSIONS

Our trial brought forward the use of Pamidronate as a measure against heightened bone resorption in our CCI cohort. The drug linked to improved clinical outcomes, keeping renal parameters stable. We're now on the lookout for prospective studies that can validate what we've

observed — show definitive causation and see whether any decline happens in osteoporotic fractures after surviving CCI. Getting into physiology, a pamidronate-triggered synthesis reduction in osteocalcin might act as a safeguard against hypoglycemia. This makes quite an intriguing example of integrative physiology at work within CCI landscapes! Our research sparks fresh insights into this complex demographic's metabolic management - largely uncharted territory—plus it adds to an underwhelming, yet gradually increasing pool of knowledge about CCIs.

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