



CODEN [USA]: IAJPBB

ISSN: 2349-7750

**INDO AMERICAN JOURNAL OF  
PHARMACEUTICAL SCIENCES**<http://doi.org/10.5281/zenodo.1413646>Available online at: <http://www.iajps.com>

Research Article

**OUTCOMES AFTER ANGIOGRAPHY WITH SODIUM  
BICARBONATE AND ACETYLCYSTEINE**<sup>1</sup>Dr. Ammara Kanwal, <sup>2</sup>Dr. Sundas Aftab, <sup>3</sup>Dr. Tazmeen Adeena Choudhry<sup>1</sup>WMO, DHQ Hospital, Layyah.<sup>2</sup>WMO, DHQ Hospital, Layyah.<sup>3</sup>PGR Medicine, DHQ Hospital, Sheikhpura.**Abstract:**

Both "Intravenous Sodium Bicarbonate" and "Oral Acetylcysteine" are extensively utilized in the cure of acute injury of kidney and accompanying contrary results after angiography deprived of any proof of their effectiveness.

In this study we use the factorial design of 2-by-2 and casually assigned 5177 renal complications at high-risk stage patients, who also have scheduled for angiography while receiving 1.26% sodium bicarbonate through intravenous or sodium chloride 0.9% with five days oral placebo: from 5177 patients, 4993 were encompassed in the adapted objective to treat assessment. Death is the primary endpoint, dialysis requirement at 90 days; accordingly, acute kidney injury was our secondary endpoint.

Sponsor blocked the trial after interim analysis which was pre-specified. At the primary endpoint, there was no link between acetylcysteine and sodium bicarbonate ( $P=0.33$ ). There was happening of primary endpoint in 110 patients from 2511 (which was 4.4%) in the group of sodium bicarbonate, if compared with 116 patients from 2482 (which was 4.7%) in the group of sodium chloride (at the odds ratio of 0.93, CI (confidence interval) 95%, 0.72 to 1.22;  $P=0.62$ ) and 114 patients from 2495 patients (which was 4.6%) in the group of acetylcysteine with the comparison of 112 of 2498 patients (which was 4.5%) in the group of placebo (with specific odds ratio, 1.02; confidence interval (CI) 95%, 0.78 to 1.33  $P=0.88$ ).

There was basically no advantage of using intravenous sodium bicarbonate over the acetylcysteine, among the patients who were at high-level renal complication risk and who were experiencing angiography.

**Keywords:** Acute Kidney Injury, Angiography, Acetylcysteine, and Sodium Bicarbonate

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Please cite this article in press Ammara Kanwal et al., **Outcomes After Angiography With Sodium Bicarbonate And Acetylcysteine.**, Indo Am. J. P. Sci, 2018; 05(09).

## 1.0 INTRODUCTION:

Severe kidney injury linked with the direction of distinction material in the time period of angiography which can result in chronic kidney disease, death, and dialysis need. Intravenous isotonic sodium in the peri-procedural administration has been considered the main prevention of this basic complication. According to this study, as per the hypotheses, urinary alkalization of sensitive oxygen varieties alleviate injury of renal “tubular epithelial-cell” from iodinated use contrast material and several studies have further evaluated the sodium bicarbonate use by intravenous specifically with intravenous sodium chloride and with unpredictable outputs evaluated treatment with acetylcysteine in acute kidney injury prevention (Bouzas-Mosquera and Recio-Mayoral, 2008).

Therefore, counterbalance regarding these involvements; besides their extensive clinical practice use. In this study, we designed a trial of (PRESERVE) “Prevention of Serious Adverse Events Following Angiography” while comparing intravenous sodium chloride with intravenous sodium bicarbonate and acetylcysteine as oral administration regarding the prevention of severe results and kidney injury in patients experiencing non-coronary and coronary angiography (Brown *et al.*, 2009).

## 2.0 METHODS:

### 2.1 Trial Design

The trial supported by the “Department of Veterans Affairs Cooperative Studies Program” in the United States of America with double-blind and placebo drug controlled. The period of this trial started from Feb. 2013 to March 2017. In this trial, all patients have been enrolled by different 53 medical centers in the US. Approval of this trial was made by “Veterans Affairs” by the Veterans Affairs Department. In the overall period of trial data monitoring and safety committee met two times yearly (Peter, 2018).

### 2.2 Trial Population

The trial population is based on the patients who experienced non-coronary and coronary angiography with 15-44.9 ml (eGFR) “estimated glomerular filtration rate” per minute as per the 1.73m<sup>2</sup> body surface area. We omitted those suffered patients who were experiencing emergency angiography and also those patients which are an unmanaged baseline of blood level creatinine (increased or decreased of  $\geq 25\%$  before angiography (Vásquez, Domínguez and Perdomo, 2017).

### 2.3 Interventions and measure of kidney function

In this study 2 by 2 factorial design has been used, we swiftly allocated entitled patients who receive 1.26% intravenous sodium bicarbonate or 0.9% sodium chloride through intravenous and acetylcysteine capsules orally or placebo capsules. In this factorial design, randomization was achieved by centralized means and was stratified as per the site of the trial. The trial investigators and patients were uninformed of the assignments of trial group (SHAVIT *et al.*, 2009).

A blood sample has been collected from every patient earlier intravenous fluid of trial initiation (baseline) and after angiography 3 to 5 days. All those patients who did not deliver the blood sample in the range of 90 to 104 days, in this trial we sustained to challenge to get the 180 days sample. All patients’ specimen has been shipped to (“Advanced Biomedical Labs”) a centralized laboratory specifically selected for the trial, in that laboratory serum creatinine was calculated concurrently in all samples taken from each patient by IDMS “isotope dilution mass spectrometry”. We gathered patients’ urine for the local magnitude of creatinine and albumin at the angiography time for pH measurement from two to four hours later than angiography (Vásquez, Domínguez and Perdomo, 2017).

### 2.4 Trial End Points

In this study, the primary endpoint is based on the requirement of dialysis, composite of death or obstinate increase from baseline up to 50% at least in the level of serum creatinine at 90 to 104 days later of angiography, with the confirmed testing period of fourteen days. We determined dialysis requirement and death by medical records reviewing and overall hospitalization in the time duration of ninety days later on angiography by family members or patients interviewing. The successive testing of creatinine was achieved by the same method means which was utilized in original sample testing (Whitcomb, 2015).

Accordingly, our secondary endpoint, related acute kidney injury considered as secondary endpoints which as prescribed as an upsurge in 25% serum creatinine or 0.5mg serum creatinine per deciliter later on angiography from 3 to 5 days baseline. Furthermore, any kind dialysis within ninety days, death within the same period and confirmed kidney impairment from 90 to 104 days and heart failure (Vásquez, Domínguez and Perdomo, 2017).

### 3.0 Statistical Analysis

In this study, we utilized an adapted treat intention assessment which encompassed all patients who had experienced randomization and assigned the interventional trial irrespective of either their

experience going angiography or not. Except for this trial, the assessment was patients who basically have never received the interventions and no history of angiography experiment. Our estimated patients were 7680 who require to be registered regarding trial to detect 90% a decrease in overall primary endpoint rate from 8.7% to intervention each trial of 6.5%, similarly presumptuous a loss of 3% to follow-up with on trial intervention interaction (Zhao *et al.*, 2016).

As an interim assessment, as pre-specified, we executed the multiple testing of "O'Brien-Fleming" process after 50% approx. of the patient's expected number had been trailed in overall 90 days. At the interim analysis period, we executed the group sequential approach to evaluate the provisional power of a basic test two proportions to the primary rate endpoint in which we assumed three multiple accrual scenarios of latest primary events over the intervention groups, according to the alpha levels regarding each situation set as 0.048 and 0.024 (Wong *et al.*, 2016).

#### 4.0 RESULTS:

For the period of Feb 2013 to Mar 2017 the overall 5177 patients (along which 4441 registered at the sites of Veterans Affairs and from George Institute

Sites are 736 numbers) endured randomization. Total of 3.6% (184 patients) were reserved after randomization (due to angiography cancellation before trial interventional receipt in 144 suffered patients and extraction of consent in 40), through which output of 4993 primary analysis patients; similarly, this group 1.1% (which are 56 patients) who basically established trial interventions but never experience angiography (Wong *et al.*, 2016).

#### 4.1 Baseline Features

From the 4993 patients, in this trial we randomly allocated 2511 which obtain sodium bicarbonate, similarly, 2482 patients obtain sodium chloride and 2495 obtain acetylcysteine and finally 2498 which obtain placebo. As per the patients, the mean ( $\pm$ SD) age was 69.8 $\pm$ 8.2 years; along with all patients 93.6% (4671) were male and 80.9% (4041) had diabetes mellitus. According to baseline, the level of median serum creatinine was 1.5 milligram as per deciliter (IQR, the range of interquartile from 1.3 to 1.8, and eGFR median was 50.2 milliliter per 1.73 m<sup>2</sup> (IQR, the range of interquartile from 41.1 to 59.4). Categorically, there were some specific patients which allocated to the group of sodium bicarbonate as compared to the group of sodium chloride with the ratio of 4.3% versus 2.9%, P=0.008 (Peter, 2018).

| Table 1. Demographic, Clinical, and Procedural Characteristics of the Patients.* |                             |                          |                         |                   |
|--|-----------------------------|--------------------------|-------------------------|-------------------|
| Characteristic   | Sodium Bicarbonate (N=2511) | Sodium Chloride (N=2482) | Acetylcysteine (N=2495) | Placebo (N=2498)  |
| <b>Demographic</b>   |                             |                          |                         |                   |
| Age — yr   | 69.9 $\pm$ 8.1              | 69.7 $\pm$ 8.3           | 70.0 $\pm$ 8.1          | 69.6 $\pm$ 8.3    |
| Male sex — no. (%)   | 2351 (93.6)                 | 2320 (93.5)              | 2347 (94.1)             | 2324 (93.0)       |
| Race or ethnic group — no. (%)†  |                             |                          |                         |                   |
| White  | 1955 (77.9)                 | 1938 (78.1)              | 1960 (78.6)             | 1933 (77.4)       |
| Black  | 271 (10.8)                  | 299 (12.0)               | 279 (11.2)              | 291 (11.6)        |
| Other  | 285 (11.4)                  | 245 (9.9)                | 256 (10.3)              | 274 (11.0)        |
| Hispanic   | 109 (4.3)                   | 72 (2.9)                 | 79 (3.2)                | 102 (4.1)         |
| <b>Clinical</b>  |                             |                          |                         |                   |
| Weight — kg  | 98.0 $\pm$ 21.8             | 98.3 $\pm$ 22.3          | 98.4 $\pm$ 22.1         | 97.8 $\pm$ 22.1   |
| Median blood creatinine (IQR) — mg/dl  | 1.5 (1.3–1.8)               | 1.5 (1.3–1.8)            | 1.5 (1.3–1.8)           | 1.5 (1.3–1.8)     |
| Median estimated glomerular filtration rate (IQR) — ml/min/1.73m <sup>2</sup>    | 50.2 (41.2–59.5)            | 50.2 (41.1–59.4)         | 50.1 (41.4–59.4)        | 50.3 (41.0–59.6)  |
| Median urinary albumin-to-creatinine ratio (IQR)‡                                | 56.3 (12.4–311.6)           | 56.4 (12.5–263.6)        | 58.3 (12.0–272.0)       | 54.4 (13.2–298.1) |
| Ratio category — no./total no. (%)   |                             |                          |                         |                   |
| <30  | 874/2262 (38.6)             | 849/2253 (37.7)          | 874/2264 (38.6)         | 849/2251 (37.7)   |
| 30 to 300  | 780/2262 (34.5)             | 857/2253 (38.0)          | 826/2264 (36.5)         | 811/2251 (36.0)   |
| >300   | 608/2262 (26.9)             | 547/2253 (24.3)          | 564/2264 (24.9)         | 591/2251 (26.3)   |
| Diabetes mellitus — no. (%)  | 2019 (80.4)                 | 2022 (81.5)              | 2011 (80.6)             | 2030 (81.3)       |
| <b>Procedural</b>  |                             |                          |                         |                   |
| Procedure type — no./total no. (%)   |                             |                          |                         |                   |
| Coronary   | 2238/2480 (90.2)            | 2228/2457 (90.7)         | 2237/2469 (90.6)        | 2229/2468 (90.3)  |
| Noncoronary  | 242/2480 (9.8)              | 229/2457 (9.3)           | 232/2469 (9.4)          | 239/2468 (9.7)    |
| Percutaneous intervention — no./total no. (%)                                    | 705/2480 (28.4)             | 701/2457 (28.5)          | 719/2469 (29.1)         | 687/2468 (27.9)   |
| Contrast type — no./total no. (%)  |                             |                          |                         |                   |
| Iodixanol  | 1404/2480 (56.6)            | 1388/2457 (56.5)         | 1405/2469 (56.9)        | 1387/2468 (56.2)  |
| Low-osmolal agent  | 1076/2480 (43.4)            | 1069/2457 (43.5)         | 1064/2469 (43.1)        | 1081/2468 (43.8)  |
| Median volume of contrast material (IQR) — ml                                    | 85 (56–135)                 | 85 (55–138)              | 85 (55–140)             | 85 (55–135)       |
| Left ventricular end-diastolic pressure — mm Hg                                  | 17.9 $\pm$ 8.1              | 18.3 $\pm$ 8.2           | 18.1 $\pm$ 8.0          | 18.1 $\pm$ 8.3    |

(Source: Schmidt *et al.*, 2017)

#### 4.2 Adherence Intervention Trial and procedural features

From 4937 patients who experienced angiography, 90.5% or 4466 experience the coronary angiography and 9.5% or 471 experienced the non-coronary angiography; total 28.5% or 1406 patients also experienced percutaneous intervention. The contrast material median volume that was managed with 85 milliliters (IQR, the range of interquartile from 55 to 137), the features process were identical in these trial groups (Schmidt et al., 2017).

The intravenous median volume flued trial was managed through 344 milliliters; (IQR the range of interquartile from 274 to 444) prior to angiography; specifically 114 milliliters (IQR the range of

interquartile from 74 to 170 in the time period of angiography and 570 milliliters (IQR range from 472 670) later angiography. Sodium bicarbonate volumes and similarly volumes of sodium chloride with the timeframe of management were same as in the groups of the trial. Later on after angiography, the pH value of mean urine was  $6.7 \pm 0.8$  in the group of sodium bicarbonate and in the group of sodium chloride was  $6.0 \pm 0.8$  ( $P < 0.001$ ). Inclusively 4050 from 4993 patients (which was 81.1%) followed the proposed routine of placebo and acetylcysteine capsules, according to the same rates of following in two groups of trials. Accordingly, there was no important variance in solemn adverse events throughout the trial groups.

**Table 2. Serious Adverse Events, with the Exclusion of Kidney-Related Events.\***

| Type of Event                                  | Sodium Bicarbonate<br>(N = 2511) | Sodium Chloride<br>(N = 2482) | Acetylcysteine<br>(N = 2495) | Placebo<br>(N = 2498) |
|--|----------------------------------|-------------------------------|------------------------------|-----------------------|
| <i>number of patients with event (percent)</i> |                                  |                               |                              |                       |
| Cardiac  | 961 (38.3)                       | 955 (38.5)                    | 951 (38.1)                   | 965 (38.6)            |
| Heart failure                                  | 201 (8.0)                        | 166 (6.7)                     | 170 (6.8)                    | 193 (7.7)             |
| Arrhythmia                                     | 97 (3.9)                         | 114 (4.6)                     | 103 (4.1)                    | 108 (4.3)             |
| Coronary event                                 | 477 (19.0)                       | 496 (20.0)                    | 498 (20.0)                   | 475 (19.0)            |
| Gastrointestinal                               | 81 (3.2)                         | 60 (2.4)                      | 81 (3.2)                     | 60 (2.4)              |
| Infectious                                     | 183 (7.3)                        | 205 (8.3)                     | 175 (7.0)                    | 213 (8.5)             |
| Neurologic                                     | 73 (2.9)                         | 77 (3.1)                      | 77 (3.1)                     | 73 (2.9)              |
| Pulmonary                                      | 116 (4.6)                        | 126 (5.1)                     | 119 (4.8)                    | 123 (4.9)             |
| Vascular                                       | 130 (5.2)                        | 120 (4.8)                     | 118 (4.7)                    | 132 (5.3)             |

(Source: Schmidt et al., 2017)

#### 4.3 Primary End Point

In this study we did not find any specific and significant collaboration between acetylcysteine and sodium bicarbonate ( $P=0.33$ ), the collaboration or interaction reference has been omitted from the logistic-regression final model. This non-existence of important collaboration was established with the utilization of a stepwise procedure, accordingly the primary endpoint happened in 4.4% (which were

110 in numbers) patients in the group of sodium bicarbonate with the comparison with 4.7% (which were 116 in numbers) patients in the group of sodium chloride (with odd ration, 0.93; with the CI of 95%, from 0.72 to 1.22;  $P=0.62$ ), and in 4.6% (114) patients in the group of acetylcysteine group with the comparison of 4.5% (112) patients in the group of placebo, odds ratio, 1.02; 95% CI, from 0.78 to 1.33;  $P = 0.88$  (Schmidt et al., 2017).

**Table 3. Primary and Secondary End Points.**

| Outcome   | Sodium Bicarbonate (N=2511) | Sodium Chloride (N=2482) | Odds Ratio (95% CI) | P Value | Acetylcysteine (N=2495) | Placebo (N=2498) | Odds Ratio (95% CI) | P Value |
|---|-----------------------------|--------------------------|---------------------|---------|-------------------------|------------------|---------------------|---------|
|   | no. of patients (%)         |                          |                     |         | no. of patients (%)     |                  |                     |         |
| Primary end point*  | 110 (4.4)                   | 116 (4.7)                | 0.93 (0.72–1.22)    | 0.62    | 114 (4.6)               | 112 (4.5)        | 1.02 (0.78–1.33)    | 0.88    |
| Secondary end points  |                             |                          |                     |         |                         |                  |                     |         |
| Contrast-associated acute kidney injury†  | 239 (9.5)                   | 206 (8.3)                | 1.16 (0.96–1.41)    | 0.13    | 228 (9.1)               | 217 (8.7)        | 1.06 (0.87–1.28)    | 0.58    |
| Death by 90 days  | 60 (2.4)                    | 68 (2.7)                 | 0.87 (0.61–1.24)    | 0.43    | 67 (2.7)                | 61 (2.4)         | 1.10 (0.78–1.57)    | 0.59    |
| Need for dialysis by 90 days  | 32 (1.3)                    | 29 (1.2)                 | 1.09 (0.65–1.81)    | 0.73    | 30 (1.2)                | 31 (1.2)         | 0.97 (0.58–1.60)    | 0.90    |
| Persistent kidney impairment by 90 days   | 28 (1.1)                    | 25 (1.0)                 | 1.10 (0.64–1.91)    | 0.71    | 26 (1.0)                | 27 (1.1)         | 0.96 (0.56–1.66)    | 0.89    |
| Hospitalization with acute coronary syndrome, heart failure, or stroke by 90 days | 272 (10.8)                  | 251 (10.1)               | 1.08 (0.90–1.29)    | 0.40    | 244 (9.8)               | 279 (11.2)       | 0.86 (0.71–1.04)    | 0.11    |
| All-cause hospitalization by 90 days  | 1071 (42.7)                 | 1052 (42.4)              | 1.01 (0.90–1.13)    | 0.85    | 1069 (42.8)             | 1054 (42.2)      | 1.03 (0.91–1.15)    | 0.64    |

(Source: Schmidt et al., 2017)

#### 4.4 Secondary End Point

The acetylcysteine and sodium bicarbonate interaction with the concern regarding contrast-link about the acute injury of the kidney was not noteworthy ( $P=0.46$ ) and was omitted from the logistic-regression final model. Acute kidney injury with contrast-associated in 9.5% (239) patients in the group of sodium bicarbonate with comparison of 8.3% (206) patients in the group of sodium chloride group (which odds ratio is 1.16; CI 95%, from 0.96 to 1.41;  $P=0.13$ ) and in 9.1% (228) patients in the group of acetylcysteine with the comparison of 8.7% (217) in the group of placebo and its odds ratio is 1.06; CI 95%, from 0.87 to 1.28;  $P=0.58$ , (Schmidt et al., 2017)

#### 5.0 DISCUSSION:

In this randomized and multinational managed trial in patients with the disease of chronic kidney who were also experiencing angiography, we elaborated no advantage of “intravenous sodium bicarbonate” over “acetylcysteine” administrated orally or “intravenous sodium chloride” over placebo administrated orally for the dialysis, death, and kidney impairment prevention at ninety days contrast-associated acute injury of kidney contrast or any other secondary level endpoints. There were several other previously maintained trials and another meta-analysis which may compared sodium chloride with sodium bicarbonate and analyzed acetylcysteine regarding the acute injury of kidney prevention and this finally shown unpredictable outputs. Besides equipoise about the efficiency of these conducts which are largely utilized in clinical practice. Therefore, many trials, similar to these interventions may have considered underpowered. In this study, our prescribed trial was blocked after the registration of 5177 patients with a pre-planned cohort of 67.4% (7680) of those patients which had experienced randomization and

4993 were comprised in our primary assessment (SHAVIT et al., 2015).

This study was restricted on the basis of population, as the patients selected with (eGFR) chronic kidney disease with the only stage of 3 or 4 of 30 to 59.9 milliliters per 1.73 m<sup>2</sup>, specifically for stage 3 and from 15 to 29.9 milliliters per 1.73m<sup>2</sup> specifically for stage 4. All those patients who are suffered from stage 3A (considered as eGFR of 45 to 59.9 milliliters per 1.73m<sup>2</sup> also need to consider diabetes mellitus, a particular condition which upsurges the acute injury of kidney risk in all those patients who have impaired function of the kidney. On the contrary, normal kidney function patients have been encompassed in multiple prior intervention trials, comprising the ACT “Acetylcysteine for Contrast-Induced nephropathy Trial (Vásquez, Domínguez and Perdomo, 2017).

#### 6.0 CONCLUSION:

In conclusion, all those patients having impaired function of the kidney who were experiencing angiography, as we found, the peri-procedural intravenous sodium bicarbonate presented no advantage over sodium chloride regarding the main adverse kidney occurrence, acute injury of kidney and death. Additionally, we also originated that there no advantage regarding acetylcysteine oral administration over placebo while considering the decline in the same risk.

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