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A low osmolarity rehydration solution that helps chemo patients.

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Abstract:

Intro: Prior research using oral rehydration solutions (ORS) have focused primarily on diarrhea secondary to infectious diseases such as cholera. We evaluated the efficacy of supplying oral rehydration solution (ORS) to patients undergoing chemotherapy.

Method: Patients undergoing one of four chemotherapy treatments (CAF, EC, FOLFIRI, or IFL), in one of eleven hospitals, with HDI scores largely representative of the global population (Range: 0.48-0.89), were divided semi-randomly into two groups. Patients in the test group received a low-osmolarity oral rehydration solution powder, and instructed to consume it with water. Patients in the control group did not get the rehydration solution. Return hospital visits were tallied for both groups during the first three months of treatment. Mean return visits per hospital, per treatment, were calculated for each group. A *t*-test for independent samples was conducted on these data points.

Results: Welch's *t* was used to make corrected group comparisons between the groups. It found a significant difference in monthly return visit rate between the control group ($M = 4.35$, $SD = 0.61$) and the test group ($M = 0.94$, $SD = 0.18$), $t(23.386) = 24.5$, $p < .001$, $d = 7.58$. The effect size of this difference was remarkably large.

Discussion: Patients who had access to the ORS had return visit rates that were less than 25% of those who did not. This reduction in hospital visits demonstrates that the medical use of appropriate ORS can be used as a supplement treatment for chemotherapy patients.

The deleterious health effects of dehydration cannot be understated (El-Sharkawy, Sahota, & Lobo, 2015). Oral Rehydration Solutions (ORS) were established as a cornerstone of therapy in the 1970's to treat patients with life-threatening dehydration that results from diarrhea, especially from cholera (Binder, Brown, Ramakrishna, & Young 2014). ORS has been repeatedly shown to be an efficacious treatment for cholera-induced diarrhea (Ververs & Narra, 2017; Kühn et al., 2014; Okeke et al., 2005), as well as diarrhea from other cholera-like sources (Gill et al., 2013; Qadri, Svennerholm, Faruque, & Sack, 2005). However, diarrhea can result from noncommunicable diseases as well.

One of the biggest current global health concerns is cancer. Cancer is expected to become a leading cause of morbidity and mortality across all major regions of the world in the next few decades (Jaspers et al., 2015; Jemal et al., 2011; Ferlay et al., 2008). Common treatment regimens for cancer include some form of chemotherapy. This drug-combination therapy prevents tumor cells from growing or reproducing, and simultaneously starves them of nutrients needed to survive (Muchmore & Wanebo, 2008). During treatment, collateral damage to vital endogenous processes abounds, and results in the destruction of cells, hormones, and enzymes, causing nausea, vomiting, and diarrhea. It can also cause adverse interactions with appetite regulating mediators in the hypothalamus (Sinno et al., 2010). This results in a disinclination to consume water or food, which exacerbates dehydration and leads to a slower, more painful recovery (Daly et al., 2016; Sullivan et al., 2018). Understandably, rehospitalization rates during chemotherapy treatments are very high (Kelly, Cajas, Baumgartner, & Lowy, 2018; Martin et al., 2016; Ang et al., 2015). To date, no study has determined the effiacy of using ORS to treat chemotherapy patients.

Method:

We developed a proprietary low-osmolarity ORS formulation, which we call R^3, based on the World Health Organization (WHO) low osmolarity salts, that replaces water and electrolytes lost through diarrhea, vomiting, and sweating. The present study tested whether administering

R^3 to patients undergoing chemotherapy treatments could reduce the rates of rehospitalization during treatment.

Setting

Data were gathered between March, 2016 and August, 2016 from 11 hospitals in 10 countries across Africa, Asia, and Europe. The Human Development Index (HDI) of these countries had a range and distribution generally representative of the global population (Range: 0.48 - 0.89). The hospitals that supplied data, and their respective countries' HDI were: National Oncology Centre, Baku, Azerbaijan (HDI: 0.75), Chonburi Cancer Hospital, Chonburi, Thailand (HDI: 0.73), Gaborone Private Hospital, Gaborone, Botswana (HDI: 0.70), Sir Thutob Namgyal Memorial Hospital, Gangtok, Bhutan (HDI: 0.61), Khartoum Oncology Centre, Khartoum, South Sudan (HDI: 0.48), Lakeshore Cancer Center, Lagos, Nigeria (HDI: 0.51), Lampang Cancer Hospital, Lampang, Thailand (HDI: 0.73), Cancer Diseases Hospital, Lusaka, Zambia (HDI: 0.59), Léon-Bérard Cancer Center, Lyon, France (HDI: 0.89), Texas Cancer Centre, Nairobe, Kenya (HDI: 0.55), and Mount Miriam Cancer Hospital, Pulau Pinang, Malaysia (HDI: 0.78).

Implementation

This study was funded by the IARC working group on cancer prevention. All patients whose data were collected were briefed on the purpose of the study and consented to having their data used. The number of return hospital visits during the first three months of treatment were tallied for use as the dependent variable. We anonymized the by-patient data, and received total rehospitalization rates per hospital per chemotherapy treatment

ORS was hypothesized to relieve the suffering of the chemotherapy patients, so we withheld ORS from only as many patients as needed to provide sufficient statistical strength for analysis. Patients (n = 798) were assigned semi-randomly to either the control group (n = 150) or the ORS group (n = 648). In the control group, patients were sent home after treatment. In the ORS group, during their first chemotherapy visit, patients were given five kilograms of R^3. This formulation has an osmolarity of 172 mOms/L, and contained an organic lemon-lime flavoring to make it more palatable. Patients were instructed to mix thirteen and a half grams for every twelve ounces of water, and to drink that solution four times daily. In the unlikely event that patients consumed all of their ORS powder, additional ORS powder was supplied during the next hospital visit.

Patients' data were collected if they were undergoing one of four chemotherapy treatment types: EC, CAF, IFL, or FOLFIRI. These chemotherapy treatments are administered in hospitals globally. Of the patients in the control group, 29 received CAF, 44 received EC, 41 received FOLFIRI, and 36 received IFL. Of the patients in the ORS group, 123 received CAF, 198 received EC, 211 received FOLFIRI, and 116 received IFL.

Data Analysis

In all but three hospitals, data were recorded for two chemotherapy treatment types. In one hospital (Léon-Bérard Cancer Center in Lyon, France), data were gathered for three types (EC, CAF, and FOLFIRI). In two hospitals (National Oncology Centre in Baku, Azerbaijan, and Sir Thutob Namgyal Memorial Hospital in Gangtok, Bhutan), data were gathered for one type (CAF). In every hospital, for each chemotherapy treatment studied, patients were assigned to both the control and the ORS group. (For patient counts per chemotherapy treatment type per hospital, see Table 1.)

To make a comparison between patients in the control group and those in the ORS group, we sought a strategy that would provide the fairest compromise between sufficiently valuing and weighting regionally specific data from hospitals that had fewer patients, as well as higher-granularity data provided by hospitals that could treat greater numbers of patients and provide more types of chemo treatments. Conveniently, the hospitals that gave us data for only one chemo treatment had fewer patients receiving that treatment. The hospital that provided three types of chemo treatments had more patients receiving each of those treatments. Thus, we aggregated patients' return visit data into means per chemo treatment per hospital. This resulted in 21 aggregated means per group. We divided these means by three to represent an average monthly visit rate.

We conducted a *t*-test for independent samples on the aggregated hospital data to determine whether there was a significant effect of the ORS on the monthly return visit rate. This was the primary aim of our study.

Further comparisons between chemotherapy treatments were conducted, however they relied on variance that was estimated from 5-6 data points per condition per group. Low degrees of freedom provided by these data have an extremely low power of 1-ß = .22. Furthermore, not all hospitals provided data on the same chemotherapy treatment types. As such, these comparisons must be treated with caution. Despite these limitations, a 2x4 factorial ANOVA was conducted to test for possible differences between the chemotherapy treatments, or for interactions between treatment type and group.

Results:

By Group Comparisons

Mean monthly return rates per chemotherapy treatment type per hospital are given in Table 2. When treating the data from all the chemotherapy treatments as belonging to one factor: either the control or the ORS group, Levene's test found that the homogeneity of variance assumption was violated, $F(1,40) = 10.623$, $p = .002$. There was more variability for visit rates in the control group ($M = 4.35$, $SD = 0.61$) compared to visit rates in the ORS group ($M = 0.94$, $SD = 0.18$). This difference is likely attributable to the smaller sample size in the control group, which was kept small purposely so as to maximally reduce the suffering of patients in our study.

Welch's t was used to make our corrected group comparisons. It found a significant difference in monthly return visit rate between the control group and the ORS group, $t(23.386) = 24.5$, $p < .001$, $d = 7.58$. The effect size of this difference was remarkably large. Based on this comparison, it appears that supplying chemotherapy patients with ORS significantly reduced their discomfort, and dramatically improved their health outcomes.

By Treatment Comparisons

When treating our data as belonging to multiple factors (Factor A being group; Factor B being chemotherapy treatment type) Levene's Test did not show a violation of the homogeneity of variance assumption at the alpha = .05 level, $F(7,34) = 1.63$, $p = .15$. Thus, a 2x4 factorial ANOVA was run without corrections. The to-be-expected main effect of the group on return visits per month $F(1, 34) = 2932.24$, $p < .001$, $\eta^2 = .92$ accounted for an overwhelming proportion of the variance. There was as well a main effect of treatment type, $F(3, 34) = 36.72$, $p < .001$, $\eta^2 = .03$ and an interaction effect of group and treatment type $F(3, 34) = 40.27$, $p < .001$ $\eta^2 = .04$. The general benefit of having ORS appears to heavily outweigh any differences between chemotherapy treatment types. As mentioned already, the low degrees of freedom provided by these data render comparisons of the treatment types unreliable, with an extremely low power of 1-ß = .22. As such, deeper analyses were not conducted. . Further research could elucidate whether there is a difference in the effectiveness for one chemotherapy treatment over another.

Discussion:

We studied a highly representative sample of patients undergoing one of several chemotherapy treatments from hospitals across almost a dozen countries. Patients who were given our low-osmolarity ORS had return visit rates that were less than 25% of those who were not. This study is the first to demonstrate such a large difference in the rehospitalization rates of chemotherapy patients as a direct result of ORS consumption.

It is worth mentioning that, prior to the official start of this study, in an unpublished pilot trial, we used an unflavored formulation of R^3. However, the native salty taste was unpalatable to most chemotherapy patients, and so they had difficulty consuming R^3 as instructed. We reformulated R^3 to include an organic, natural lemon flavoring to improve its palatability. Once the flavoring was added, patients no longer complained about the taste, and the clinical trials could be carried out properly.

The World Health Organization (WHO) concluded that a lower-osmolarity ORS formulation was needed to replace the previous hypo-osmolar formulation. This switch was motivated by improved medical outcomes, including reductions in stool output, vomiting, and the need for supplemental intravenous (IV) therapy (Binder et al., 2014; Duggan et al., 2004). The WHO lower-osmolarity ORS has an osmolarity of 245 mOsm/L. Our proprietary low-osmolarity formulation, R^3, has an even lower osmolarity of 172 mOsm/L. R^3 was highly successful in reducing hospital visit rates. It is possible that the WHO ORS could be successful to this end as well.

Cancer affects people of every socio-economic status, but results in higher mortality rates among lower HDI countries (Ferlay et al., 2015). These countries also have higher rates of mortality resulting from diarrhea (Santosham et al., 2010). ORS provide a cost-efficient treatment option, but budgetary, logistical, and bureaucratic concerns have made it difficult to improve the channels by which ORS are administered (Wilson et al., 2013; Isanka et al., 2012; Santosham et al., 2010; Walker, Fontaine, Young, & Black, 2009). Chemotherapy treatment may represent an avenue that can attract policy makers to improve access to ORS more generally.

Advances in hygiene, public awareness, and sanitation continue to reduce the infection and transmission rate of infectious diarrheal diseases (Jahan, 2016), and have lessened the prevalence of infection-related cancers in less developed countries. However, there have been simultaneous increases in cancers caused by dietary, hormonal, and reproductive factors (Bray, Jamal, Gray, Ferlay, & Forman, 2012). It is possible that the number of

chemotherapy treatments will continue to increase. Our ORS formulation has been shown to help patients undergoing these treatments.

It is our hope that our findings will aid in motivating lawmakers to improve distribution channels for ORS, and encourage practitioners to consider using ORS to treat more diverse dehydrating maladies.

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Table 1:

Patient counts per treatment per hospital.

	Control				**ORS**			
City	**CAF**	**EC**	**FOLFIRI**	**IFL**	**CAF**	**EC**	**FOLFIRI**	**IFL**
Baku	3				16			
Chonburi	6	14			24	36		
Gaborone	6			6	21			38
Gangtok	3				17			
Khartoum	4		5		14		52	
Lagos		6		8		45		28
Lampang			13	6			38	19
Lusaka		6		7		41		22
Lyon	7	14	10		31	48	56	
Nairobi		4	7			28	26	
Pulau Pinang			6	9			39	27
Total	29	44	41	36	123	198	211	134

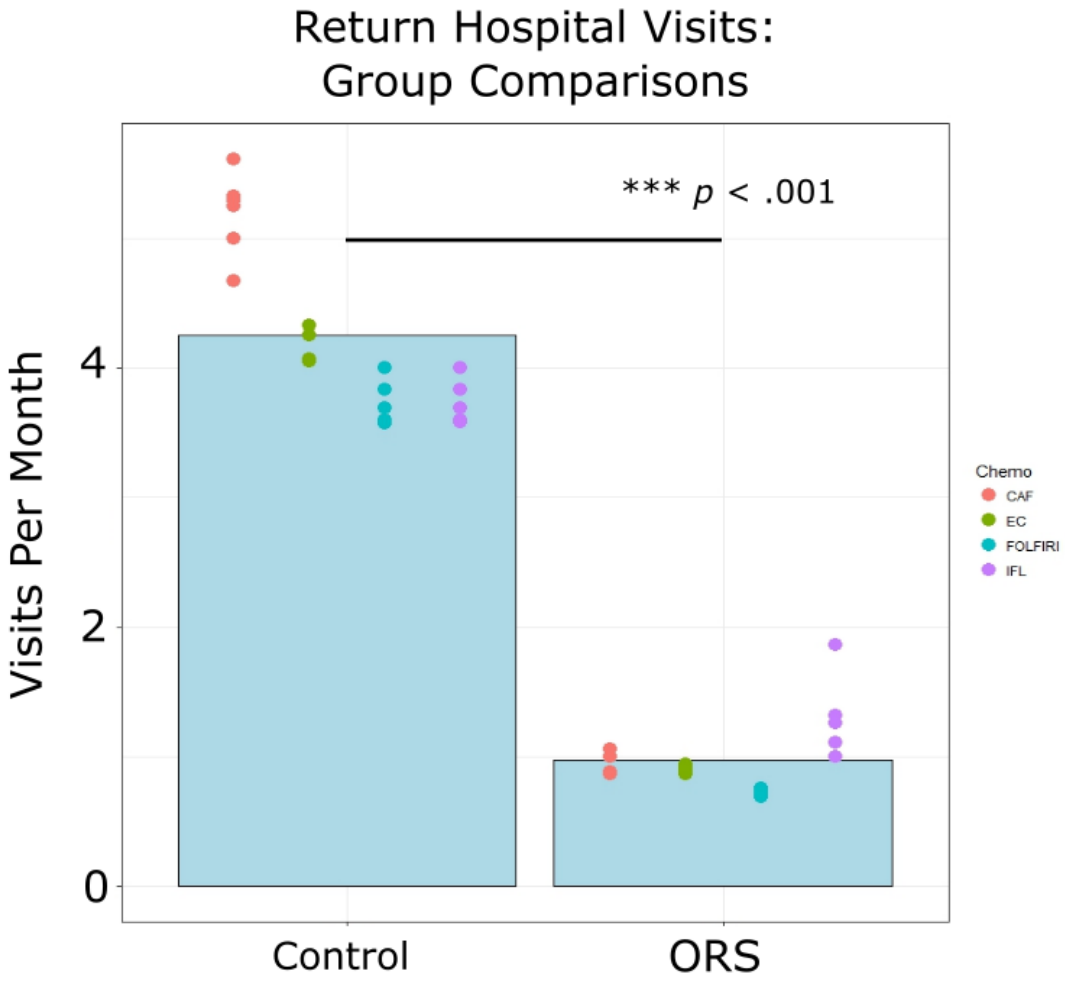
Table 2:

Mean monthly visits per treatment per hospital.

	Control				**ORS**			
City	**CAF**	**EC**	**FOLFIRI**	**IFL**	**CAF**	**EC**	**FOLFIRI**	**IFL**
Baku	4.67				1			
Chonburi	5	4.07			0.88	0.94		
Gaborone	5.61			4.33	1			1.32
Gangtok	5.33				1.06			
Khartoum	5.25		4		0.86		0.75	
Lagos		4.5		4		0.86		1.11
Lampang			3.69	4			0.71	1.26
Lusaka		4.33		3.86		0.90		1
Lyon	5.29	4.07	3.6		1	0.92	0.70	
Nairobi		4.25	3.57			0.86	0.70	
Pulau Pinang			3.83	4.11			0.74	1.19
Mean	5.19	4.24	3.73	4.06	0.97	0.90	0.72	1.18

Figure 1:

Patients who were given ORS had far fewer return visits than patients who were not.



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