Intravenous fluids for pain management in head and neck cancer patients undergoing chemoradiation

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Contributions: (I) Conception and design: CI Rivers, AK Singh; (II) Administrative Support: AK Singh; (III) Provision of study materials or patients: AK Singh; (IV) Collection and assembly of data: CI Rivers, AJ Iovoli; (V) Data analysis and interpretation: AJ Iovoli, U Chatterjee, GM Hermann; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Pain due to oral mucositis affects the majority of patients receiving chemoradiation (CRT) for head and neck cancer (HNC), and often results in dehydration. Anecdotally, intravenous (IV) fluids administered during treatment for the resultant dehydration was found to alleviate this pain. The purpose of this retrospective study was to evaluate the effectiveness of IV fluids as a method pain management in this patient population.

Methods: Patients with oral mucositis pain, secondary to CRT for HNC, were given IV fluids according to standard clinic protocol. Patients were evaluated using orthostatic vital signs and prospectively surveyed pre- and post-IV fluid administration, which included the Visual Analog Scale (VAS) for pain. Difference in pain pre- and post-IV fluid administration was evaluated using a two-tailed paired Student's *t*-test.

Results: Twenty-four patients with a total of 31 fluid administrations was available for analysis. Twenty-three patients were receiving or had recently completed CRT. One patient was receiving radiation alone. Six instances of fluid administration were excluded due to: refusal to complete the survey, concurrent pulmonary embolism, concurrent pain medication, and drug seeking behavior. Average pain score decreased from 6.5 [standard deviation (SD) 2.1] prior to IV fluids to 4.0 (SD 2.4) following fluid administration (P<0.001).

Conclusions: To our knowledge, this is the first report directly correlating IV fluid administration with pain relief, even in the absence of orthostasis. Our findings indicate that in patients undergoing CRT for HNC, the use of IV fluids alone was effective in acutely and significantly reducing pain secondary to oral mucositis.

Keywords: Oral mucositis (OM); radiotherapy; chemotherapy; patient-reported outcomes

Submitted May 14, 2020. Accepted for publication Sep 11, 2020.
doi: 10.21037/atm-20-3910
View this article at: http://dx.doi.org/10.21037/atm-20-3910

Introduction

Pain due to oral mucositis (OM) affects approximately 80% of patients who receive chemoradiation (CRT) for head and neck cancer (HNC), and can significantly impact quality of life (1). Pain scores generally increase during treatment, with a noticeable increase near the mid-point of radiation therapy that correlates with worsening mucositis, possibly exacerbated by administration of chemotherapy (2). OM leads to increased hospitalizations, aspiration risk, prolonged recovery, treatment breaks, and increased medical care costs (3-7). Extreme pain and dysphagia often lead to anorexia and dehydration, necessitating the placement of feeding tubes (8,9). Most OM therapies rely on symptom management with treatments ranging from oral rinses to low-level laser therapy (10). Opioids are often

necessary for pain management but fail to provide complete relief for many patients (11-13).

Thus, there is a need to investigate supplemental pain management strategies. In HNC patients, OM pain often leads to decreased fluid intake resulting in clinically significant dehydration; this manifests as orthostasis and/or decreased renal function, which necessitates the administration of intravenous (IV) fluids. However, even in the absence of clinically significant dehydration at the midpoint of CRT, recent data from bioelectrical impedance studies demonstrates a positive correlation between increased dehydration and the grade of OM (14). This suggests that IV fluid administration at the midpoint of CRT, even in the absence of clinical dehydration, may alleviate OM pain. The purpose of the current study is to evaluate the role of IV fluids in OM pain management in patients undergoing CRT for HNC.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3910).

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Roswell Park Comprehensive Cancer Center Institutional Review Board (EDR-103707) and informed consent was taken from all individual participants. Patients on treatment or who had recently completed radiation for HNC were evaluated for pain during routine clinical evaluations. All patients were undergoing definitive radiation therapy, the details of chemotherapy and radiation at our institution have been previously described (15,16). Our institutional practice was to prescribe prophylactic gabapentin for all patients to start at the beginning of treatment, with doses starting at 300 mg daily and titrating up to 900 mg three times daily, as tolerated. Subsequent, clinically significant pain was treated per our institutional standard of care, which consisted of acetaminophen/hydrocodone 7.5 mg/325 mg per 15 mL elixir taken up to four times per day. A fentanyl transdermal patch was prescribed for long acting pain control after short acting opioids were used 3 to 4 times per day, with acetaminophen/hydrocodone for breakthrough. Fentanyl was started at 25 µg/h and titrated up 100 µg/h as needed.

At any time during radiation treatment and at any point in a patient's analgesic regimen, patients with pain attributed to OM were given IV fluids as per standard clinic protocol. IV fluids typically consisted of 1–2 liters of lactated Ringers (LR). All patients' laboratory record and medical history was reviewed prior to IV fluids. In patients with a history of heart disease, clinical judgment was used to evaluate for any signs or symptoms of volume overload, which would have precluded IV fluids. Patients were routinely monitored by a nurse during fluid administration, and vital signs (including pulse oximetry) were measured after administration and prior to discharge from clinic. Furthermore, adequate time (at least 72 h) was allowed between reconsideration of additional IV fluids. Concurrent pain medication (beyond the standard prescribed outpatient pain medication available to the patient) was not provided with fluid administration.

Patients were evaluated with a survey immediately prior to and following IV fluid administration; the survey included a Visual Analog Scale (VAS) to determine pain level. The VAS was chosen as it has been previously validated in the setting of acute pain (17-20). Orthostatic vital signs were measured prior to and following fluid administration. Patient pain medication regimen and medications received during fluid administration were recorded at each interval.

Statistical analysis

Pain scores were reported as mean and standard deviation (SD). The difference in pre-, post- and follow-up IV fluid administration pain scores was evaluated by two-tailed paired Student's *t*-test using GraphPad Prism (Version 7.04 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com).

Results

Table 1 shows baseline patient, tumor and treatment characteristics. Twenty-four patients were available for analysis with 37 fluid administrations. Six instances of fluid administration were excluded for the following: 1 patient refused to complete the survey, 1 patient was subsequently found to have a pulmonary embolism as the source of his pain, 2 patients received concurrent IV Toradol with fluids, and 2 instances in one patient who complained of nausea and exhibited drug seeking behavior. After exclusions, a total of 31 fluid administrations were available for analysis. Twenty-three patients were either receiving or recently completed CRT. One patient received radiation alone. All patients were experiencing head and neck pain at least partially attributed to OM. Twenty-one of 24 (88%)

Table 1 Patient age, tumor, and treatment characteristics

Variables	Value
Age (y), median [range]	63 [48–83]
T stage, n [%] (AJCC 7th ed.)	
Recurrent	1 [4]
T0	0
T1	3 [13]
T2	11 [46]
T3	7 [29]
T4	2 [8]
N stage, n [%] (AJCC 7th ed.)	
Recurrent	1 [4]
N0	3 [13]
N1	3 [13]
N2a	6 [25]
N2b	6 [25]
N2c	2 [8]
N3	2 [8]
Primary tumor site, n [%]	
Nasopharynx	1 [4]
Oropharynx	18 [75]
Oral cavity	1 [4]
Larynx	3 [13]
Thyroid	1 [4]
Volume of elective radiation, n [%]	
Unilateral	7 [29]
Bilateral	15 [63]
None	2 [8]

patients were prescribed prophylactic gabapentin, as per our institutional standard. Four patients received multiple fluid administrations (range, 2–4). There was a minimum of 72 h between fluid administrations with a median time of 9 days (range, 3–32 days). No patients received supplemental nutrition via feeding tube at the time of fluid administration.

Of the 23 patients included in the analysis: 8 were found to have orthostatic hypotension prior to fluids, 13 were not orthostatic, and data was unavailable for 2 patients. All patients included in the analysis reported a decrease

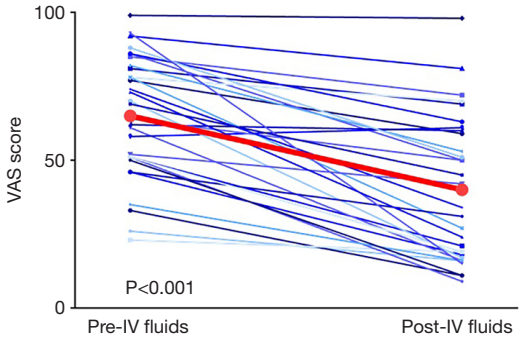

Figure 1 Spaghetti plot of pain scores before and after IV fluids. Each blue line represents a single IV fluid administration. The red line represents change in mean pain value for all 31 IV fluid administrations. IV, intravenous.

in pain. The mean pain score prior to and following IV fluid administration was 6.5 (SD 2.1) and 4.0 (SD 2.4), respectively (*Figure 1*) (P<0.001). The follow-up mean pain score (within 8 days) was available for 22 of the 23 patients and was 6.2 (SD 2.2); follow-up mean pain score was not statistically different from baseline (P=0.57). There was no difference in pain scores based on prophylactic gabapentin use (P=0.55).

Discussion

Pain scores using the VAS showed a statistically and clinically significant acute decrease following IV fluid administration. This is the first study to our knowledge documenting the effect of IV fluid administration on OM pain.

Our data is consistent with findings of Brzozowska *et al.*, who showed that HNC patients in the middle of CRT with Grade 3 versus Grade 2 OM had reduction in multiple measures of hydration as measured by bioelectrical impedance (14). Expectedly, consistent with going from Grade 3 to Grade 2 OM, patient-reported pain did not completely resolve in our study; rather, the pain persisted to a milder degree.

Despite the work of Brzozowska *et al.*, the precise mechanism of pain relief following IV fluid administration in OM is not known. The use of IV fluids has been investigated in other contexts, such as for utility in improving pain, nausea, vomiting, hydration symptoms, and postoperative morbidity, albeit with mixed results (21-26).

IV fluid administration in the pre- and post-operative setting for symptom management has been investigated

in several clinical trials. In a randomized controlled trial of 120 pediatric patients undergoing strabismus surgery, the combination of dexamethasone and IV LR was found to result in a delay in analgesic requirement, less total acetaminophen use, and significantly lower pain as measured by the VAS (21). Richer *et al.* randomized pediatric patients to IV fluids with or without the expectation of a pain medication. The authors found that the reduction in pain with IV fluids was relatively small, although a small number of patients did experience some headache relief (27). Spencer *et al.* evaluated 100 patients undergoing gynecologic surgery and found 1 L IV sodium lactate solution significantly improved dizziness and nausea (25). Cook *et al.* conducted a randomized double-blind trial in a similar group of patients and found that IV fluid administration intra-operatively, resulted in a significant reduction in the number of patients who required post-operative medication (including pain medications and antiemetics) and led to more patients ready for discharge at 3 h (22). This correlates with our observation that there is a statistically and clinically significant improvement in patient pain level without a need for additional pain medication following IV fluid administration. This observation holds true even in patients who do not present with orthostasis.

Limitations

Though our study had a small sample size, the results are highly significant and unlikely to have been changed. However, there are other limitations to our study. The nature of the IV fluid intervention makes it impossible to give a sham treatment. Consequently, while VAS is well-validated for acute pain, we cannot exclude the possibility of a placebo effect impacting the patient's subjective pain assessment. Importantly, at follow up evaluation, pain had increased in most patients, although not back to average initial pain score. This indicates that although there is possibly some lasting pain relief benefit from IV fluid administration, continuation of standard pain medications remained necessary.

Conclusions

Patients at the mid-point of CRT for HNC benefit from the administration of IV fluids with significant and acute alleviation of acute pain from OM. This holds true even in the absence of orthostasis. The routine use of IV fluids at this time point should be considered as an additional component of the pain management strategy in this population. The pain relief derived from this effect may last several days. IV fluid administration can delay but cannot replace standard pain medications. Multiple administrations of IV fluids should not be prescribed without the proper clinical and laboratory evaluation or in place of appropriate pain medications.

Acknowledgments

The authors thank Kelsey Smith PA for her tireless efforts to provide excellent care for these patients.

Funding: This work was supported by the National Cancer Institute Cancer Center Support Grant (P30CA016056). Funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Dr. Mukund Seshadri) for the series "Head and Neck Cancers – Disease Biology, Diagnostics, Prevention and Management" published in *Annals of Translational Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-3910

Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-20-3910

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3910). The series "Head and Neck Cancers – Disease Biology, Diagnostics, Prevention and Management" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Roswell Park Comprehensive Cancer Center Institutional Review

Board (EDR-103707) and informed consent was taken from all individual participants.

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Cite this article as: Rivers CI, Iovoli AJ, Chatterjee U, Hermann GM, Singh AK. Intravenous fluids for pain management in head and neck cancer patients undergoing chemoradiation. Ann Transl Med 2021;9(10):912. doi: 10.21037/atm-20-3910

