Buprenorphine: Opioid Agonist-Antagonist Benefits for Opioid Resistant Pain, Uncontrolled By Full-Agonist Opioids During Hematopoietic Stem Cell Transplant for Sickle Cell Disease

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BACKGROUND

- **Bone marrow transplant (BMT) offers potential cure for cancer and a spectrum of otherwise incurable diseases. However, the BMT complications lead to multi-systemic PAIN presentation.**
- Sickle cell disease (SCD) is a hematologic disease with life-long pain from infancy. Because of frequent pain resulting in hyperalgesia and chronic opioid use, SCD patients undergoing BMT often experience excruciating pain uncontrolled by rapid escalation of opioid dosing and numerous adverse effects.

Pain Related to BMT:
- Neuropathic Pain / Paresthesia / Headache
- Myalgia / Arthralgia / Bone Pain / Visceral Pain
- Mucositis Pain / Dyspepsia / Dysphagia / GVHD
- Inflammatory-Infection Pain / Radiation Injury Pain

Repetitive Exposure to Pain and Opioids Results In:
Opioid dose escalation → More side effects → CHRONIC pain → Central sensitization → fear, anxiety → ED / hospitalization

- **Buprenorphine, an opioid with novel pharmacology**
  - **Partial Mu opioid Receptor AGONISM – High Affinity→ Less respiratory depression, Less euphoria, Slows tolerance, Less constipation, Leaves room for other opioids**
  - **Kappa opioid receptor ANTAGONISM → Anxiolytic, ⇓addictive potential, ⇓immunosuppression, ⇓constipation**
  - **Delta opioid receptor ANTAGONISM →⇓GI and respiratory SE**
  - **Opioid Receptor Like 1 (ORL1) AGONISM → Preferred SPINAL Receptor action >> CNS R →⇓rewarding effect,⇓tolerance**
- ❖ **SAFE in renal insufficiency and hepatic impairment.**
- ❖ **Significantly decreases acute care utilization.**

OBJECTIVES

Growing body of literature have shown superior effect of **buprenorphine, Opioid Agonist-Antagonist**, over full-agonist opioids for chronic SCD pain in the outpatient setting.

A pilot prospective clinical trial for **buprenorphine-based inpatient pain management** was conducted for SCD patients' acute severe pain to assess for the inpatient use efficacy of buprenorphine in the setting of BMT, a significant pain escalation factor.

This trial was initiated after observing serial cases of SCD patients' BMT-related pain, uncontrollable by enormous doses of traditional opioids, remarkably resembling some patients with hematologic malignancy undergoing BMT.

METHODS

- Buprenorphine was started as scheduled and as-needed analgesics IV, supplemented by full-agonist opioids for SCD patients enrolled in clinical trials with BMT upon consultation for uncontrolled pain.
- **Patients' 24-hour opioid requirement** by morphine equivalent daily doses (MEDD) were assessed at **3 time points**. (Table 1)
  1) Before pain escalation; **2)** Consultation day for pain; **3)** Discharge day
- MEDDs were retrospectively compared to those of SCD patients treated with full-agonist opioids only during their BMT admission.

RESULTS

Table 1. Morphine Equivalent Daily Dose (MEDD) for BMT Pain Management in SCD Patients Receiving Full-Agonist Opioids vs. Buprenorphine-Based Management

MEDD: 24hr Opioid Requirement	Case	Pre-Consultation MEDD: Immediately Prior to Pain Escalation	Consultation Day MEDD: Pain Uncontrolled	Discharge Day Post-BMT MEDD: Pain Controlled (% Increase in MEDD)
Full-Agonist Opioid Analgesic Regimen	1	240 mg	840 mg	3192 mg (1230%)
	2	74 mg	170 mg	1220 mg (1548%)
	3	10 mg	352 mg	1640 mg (16300%)
Buprenorphine Based Opioid Regimen	4	30 mg	40 mg	125 mg (317%)
	5	7.5 mg	22.5 mg	24 mg (220 %)

Table 2. Patient Demographics and Disease

Case	Age	Gender	Ethnic Background	Genotype
1	18	M	Nigerian	HgbSS
2	22	M	Nigerian	HgbSS
3	39	F	Congolese	HgbSS
4	19	M	African American	HgbSS
5	7	M	African American	HgbSS

RESULTS

- **Cases treated only by full-agonist** opioids (morphine / fentanyl hydromorphone / methadone / hydrocodone / oxycodone) had **escalation of MEDD by 1230 - 16300%** by discharge date compared to the time point immediately prior to escalation of BMT-related pain.
- **Buprenorphine-supported** cases had **remarkably smaller MEDD increase by 220 - 317%. (Table 1)**

CONCLUSIONS

- Our data suggests the benefits of potent pain control and limiting opioid tolerance by using Buprenorphine prior to full-agonist opioid dose escalation during BMT admission for SCD patients.
- Buprenorphine may provide the advantages for treating pain of non-SCD patients with complex pain background and experiencing difficult pain management during BMT due to pre-existing hyperalgesia and high opioid-tolerance, specifically cancer patients.
- We plan to develop a clinical trial of Buprenorphine-based complex pain management for cancer patients to compare with SCD cohort undergoing BMT.

REFERENCES

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