Case Report

Anesthesia & Pain Research

Dose Concomitant Use of Ketamine During Prostate Brachytherapy Augment Anti-Neoplastic Effects Reducing Prostate Specific Antigen?

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Received: 01 January 2018; Accepted: 28 January 2018

Citation: Larry M. Manders, Matthew Villerot, Sean Ohanian. Dose Concomitant Use of Ketamine During Prostate Brachytherapy Augment Anti-Neoplastic Effects Reducing Prostate Specific Antigen?. Anesth Pain Res. 2018; 2(1): 1-3.

ABSTRACT

Background: *Previous studies have demonstrated Ketamine to induced apoptosis in various cellular lines. Ketamine is commonly utilized during total intravenous anesthesia in patients undergoing brachytherapy for prostate cancer. The primary aim of this study was to determine if concomitant ketamine exposure during prostate brachytherapy improved outcomes evaluate through follow prostate specific antigen (PSA) levels.*

Methods: *A retrospective analysis of 91 prostate brachytherapy performed at our institution from 2014-2016 was done identifying 31 procedures in which ketamine was administered during the procedure. Measured outcomes were the comparison reduction of PSA levels at 1 month, 6 months, and 12 months post procedural visits.*

Results: *No statistical significant reduction in the prostatic specific antigen or the corresponding percent reduction of PSA levels were demonstrated between ketamine and non-ketamine exposed patient undergoing prostate brachytherapy.*

Conclusions: *Concomitant ketamine exposure does not appear to enhance the therapeutic effect of prostate brachytherapy. When comparing the overall percent reduction of PSA levels between the two groups (ketamine exposed/ no exposure), the ketamine patients did have greater decrease in PSA levels, but was not statistically significant. With the limitation of our retrospective analysis, further double blinded prospective trials may be warranted.*

Keywords

Ketamine, Brachytherapy, Prostate, Prostate Specific Antigen (PSA).

Introduction

Recently, interest has arisen as to whether anesthetic techniques can affect outcomes in patients who are undergoing oncologic procedures/surgeries [1-4]. Previous studies have demonstrated Ketamine to induced apoptosis in various cellular lines [5-7]. Ketamine, has also been proven useful in providing sedation in patient undergoing painful oncologic procedures [8,9]. With its common utilization and proapoptotic effects, the question arose as to whether ketamine may augment outcomes in oncological procedures such as brachytherapy. To date there has been a paucity of literature discussing the topic. We present a retrospective study investigating whether intraprocedural ketamine exposure during prostate brachytherapy augments treatment response as measured by prostate specific antigen (PSA) levels at one, six, and twelve-month post-operative intervals.

Materials and Method

After Institutional Review Board approval, a retrospective medical record analysis of prostate brachytherapies performed under sedation, with and without ketamine, was performed from January 1st, 2006 to December 31st 2016. Inclusion criteria consisted of

Males, of all ages greater 18 years of age undergoing brachytherapy under spinal anesthesia with sedation in which PSA was routinely monitored. Patient data was collected and record through secure share point site.

The primary outcomes measured were the reduction in PSA levels at 1 month, 6 months, and 12 months visits. Additional patient data collected were Age, American Society of Anesthesiologist Physical Status, Brachytherapy Dose, Pretreatment PSA, Grade of Prostate Cancer, and Ketamine exposure.

Statistical Analysis

A total of 91 cases of prostate brachytherapy occurred during the period examined. An analysis test was used to determine study power (Goodness of fit test-contingency tables: a prior- required sample size- given α=0.05, power 1-β = 0.95 and effect size= 0.2 small-medium). Normality/distribution of data was evaluated by histogram and probability plots. Chi square analysis was used to compare categorical data. An unpair T- Test was used to compare PSA levels between ketamine and unexposed patients. For non-parametric data, the Kruskal-Wallis and Mann Whitney tests were used.

Results

There were 91 prostate brachytherapies performed between January 2012 and December 2016. Of those, seventy-eight, three were excluded due to lack of follow up PSA levels. Of the 91 patients included in the study, 31 were concomitantly provided ketamine during brachytherapy whereas 60 were not. The mean age and Gleason score were identical between the two groups; 64 years of age with Gleason score of 7 (3+4). Patient demographics/ brachytherapy dosing described in table 1. Individuals who underwent concomitant ketamine dosing on average received 36 mg or 0.4 mg/kg. The corresponding average pretreatment PSA for each group were 6.2 ketamine versus 8.9 non-ketamine.

	No Ketamine	Ketamine	P- Value
Number of Patients	60	31	-
Average Age	63 (+/- 8)	63 (+/- 8)	0.10
ASA Status	ASA 2 = 27 ASA 3 = 33	ASA 2 = 14 ASA 3 = 17	0.26
Average Cancer Grade	7 (3+4)	7 (3+4)	0.21
Average Brachytherapy Treatment Dose	34 (+/- 18)	30 (+/- 15)	0.13

Table 1: Patient Demographics and Cancer Staging.

Upon assessment of post procedural PSA levels and PSA percent reduction from pretreatment PSA the following results were determined. At 1 month, the ketamine group had an average PSA of 1.78 resulting in a percent decrease of 61.3. This contrasts with the non-ketamine exposed group with corresponding values of 2.62, 60.3%. At 6-month follow the ketamine versus non-ketamine were correspondingly (1.07, 77.3%) and (1.82, 71.9%). Furthermore, at 12-months the ketamine versus non-ketamine groups had post procedural PSA of 0.76 and 2.04 resulting in a percent reduction of 83.6% for patient exposed to ketamine versus 71.5% for those who were not.

The group of individuals exposed to ketamine had an overall lower PSA score and greater percent PSA reduction, but upon analyses all P-values were greater than 0.05% indicating no statistical significance. The results are summarized in table 2.

	No Ketamine	Ketamine	P- Value
Average Ketamine Dose (total/dose per kg)	0/0	36/0.4	-
Starting PSA prior to Treatment	8.9 (STD 10.2)	6.2 (Std 2.8)	0.18
PSA 1 month	2.62	1.78	0.19
PSA 1 month % Reduction	60.3	61.3	0.30
PSA 6 months	1.8	1.07	0.17
PSA 6 month % Reduction	71.9	77.3	0.37
PSA 12 months	2.04	0.76	0.15
PSA 12 month % Reduction	71.5%	83.6	0.08

Table 2: Drug Dosing, Preprocedural PSA, and Results.

Discussion

As previously stated recent interest has arisen as to whether anesthetic techniques can affect outcomes in patients who are undergoing oncologic procedures/surgeries. Christopherson et al., demonstrated epidural supplementation during surgical resection was associated with enhanced short-term survival amongst colon cancer patients without metastases [1]. Furthermore, Exadaktylos et al., showed that paravertebral anesthesia and analgesia for breast cancer surgery reduced the risk of recurrence or metastasis during the initial years of follow-up [2]. These studies opened the door to the idea that anesthetic techniques could alter efficacy of oncological procedures.

A study by Biko et al. demonstrated anesthetic technique influenced cancer recurrence in individuals undergoing radical prostatectomy surgery. Within the study, patient who received an epidural plus general anesthesia group had an estimated 57% lower risk of recurrence compared with the general anesthesia plus opioids [3]. The theory behind the findings of these studies suggest surgery decreases host immune response and therefore increases risk for development of metastases. Regional anesthetic technique may reduce the immunosuppressive effect of surgery. Furthermore, improve analgesia via regional anesthesia may decrease opioid consumption which may inhibit immune defenses.

While prior studies demonstrated regional anesthesia may improve oncological procedure outcomes in terms of short term survival and reoccurrence of metastasis, there are limited studies assess individual drugs. Ketamine has been shown to induce apoptosis in various cellular lines [5-7]. Wang et al., demonstrated ketamine interaction in N-methyl-D-aspartate (NMDA) receptor increased apoptosis in neuronal tissue within rat forebrain models [5]. Whereas Braun et al., and Lee et al. demonstrated ketamine to induces apoptosis via mitochondrial pathways in respective human

lymphocytes and hepatocytes [6,7]. This is of interest as it is hypothesized by our group that ketamine may create a proapoptotic environment for cancer cells being excised or challenged during oncological procedures. Factors this with the fact ketamine has been shown beneficial in providing procedural sedation for painful oncology procedures [8,9] and its NMDA antagonism may lead to decrease opioid consumption which may prevent further inhibition of immune cells.

Our study aimed at assessing whether concomitant ketamine exposure enhance the therapeutic effect of prostate brachytherapy through comparison of post procedural PSA levels. When comparing the overall percent reduction of PSA levels between the two groups (ketamine exposed/ no exposure), the ketamine patients did have greater percent reduction in PSA levels, but the change was not statistically significant. There was no statistically significant difference in PSA or recent reduction from pretreatment PSAs at one, six, or twelve months follow up. Our concern is our study does have its limitations.

Limitations to our study include the fact it is retrospective in design. Patients were not randomly assigned in their exposure or lack thereof of ketamine. Furthermore, the dose of ketamine was not standardized. Individuals receiving ketamine on average received a total of 36 mg or 0.4mg/kg, but there was a large degree of variation between patients. With the limitations of our retrospective analysis, further double blinded prospective trials may be warranted.

Conclusion

While ketamine has previously been demonstrated to have proapoptotic effects our study failed to demonstrate that concomitant ketamine exposure during prostate brachytherapy increased the reduction of PSA levels when compared to non-exposed patient. When comparing the overall percent reduction of PSA levels between the two groups (ketamine exposed/ no exposure), the ketamine patients did have greater decrease in PSA levels, but was not statistically significant. With the limitation of our retrospective analysis, further double blinded prospective trials may be warranted.

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