Project Title: Prospective longitudinal study on the treatment outcomes of various treatment modalities under a standardized treatment protocol in patients suffered ketamine-induced voiding dysfunction (BDF 110010)

Project Co-ordinator:

Professor Chi-Fai Ng

Professor, Division of Urology, Department of Surgery, The Chinese University of Hong Kong

Team Members:

Dr Samuel CH Yee

Resident Specialist, Division of Urology, Department of Surgery, The Chinese University of Hong Kong

Dr Peter YH Tam

Consultant, Division of Paediatric Surgery and Paediatric Urology, Department of Surgery, Prince of Wales hospital

Ms Franco PT Lai

Nurse, Youth Urology Treatment Centre, Department of Surgery, The Chinese University of Hong Kong

Ms Kim WM Lee

Senior Research Assistant, Division of Urology, Department of Surgery, The Chinese University of Hong Kong

Executive summary:

Background & Objective

With the increase in recreational usage of ketamine over the world, ketamine-induced voiding dysfunction (KIVD) is becoming an important medical problem. However, while the clinical manifestation of the condition is becoming better defined, the underlying pathophysiology is still poorly understood. Moreover, majority of the current treatment is based on the experience on some small case series and there is no treatment data for larger patient sample or standard recommended treatment in the literature. With the rapid increase in patients' demand, there is an urgent need for better clinical study on the effect of various treatment regimes for the condition, to provide more evidence-based recommendation for them. Therefore, we would like to prospectively study the treatment result of various treatment modalities under a standardized treatment protocol. We hope our results would help to evaluate the effectiveness and also tolerability of various proposed treatment options in KIVD.

Methods

This is a prospective case series including all patients who attended our centre for ketamine related urological problems. Management for the patients include a 4-tier approach, namely anti-inflammatory drug / anti-cholinergic, opioid analgesic / pregabalin, intravesical hyaluronic acid, and finally surgical intervention including hydrodistension and augmentation cystoplasty. Outcome was assessed by standard questionnaires [Pelvic pain-urgency-frequency (PUF) symptom scale, EuroQol Visual Analogue Scale (EQ VAS) and general response assessment (GRA)] and also urine flow study. Also the adverse effect of the treatment was also recorded. Moreover, possible predictive factors for treatment outcomes would also be assessed.

Results

Between December 2011 and June 2014, 463 patients attended our clinic for KIVD, with 294 of them having their first assessment during the project period (1st July 2012 to 30th June 2014), and all were managed by the same team with the same standardized protocol. Amongst these patients, 319 patients came back for follow-up assessment. Overall mean follow-up duration was 10.7 ± 8.5 months, with 126 patients have follow-up more than 1 year. For those patients who received first line treatment (290 patients) with at least one follow-up in our centre, 202 (69.7%) patients reported improvement in symptom, 46 (15.9%) patients reported similar symptom and 42 (14.5%) reported worsening of treatment. There was also significant improvement in PUF scores, quality of life score and also voided volume. Both abstinence from ketamine usage and the amount of ketamine consumed were factors predicting the improvement of PUF scores. For those patients who required second line oral therapy (62 patients), 42 (67.7%) patients reported improvement in symptom, with significant improvement in PUF scores, quality of life score and also voided volume. The amount of ketamine usage per week, abstinence status and baseline symptom scores were significant factors in predicting patients' need for second line therapy. Eight patients have completed the intravesical therapy. Besides there was a significant improvement in voided volume for the patients after treatment, 5 of them could step down their oral medication usage. There were 109 patients reported adverse effects reported and most of them were mild and related to the use of anticholinergic agents. No adverse effect was reported after second and third line treatment.

Conclusion

The study demonstrated the efficacy of managing ketamine induced voiding dysfunction using a standardized treatment protocol. Both anti-inflammatory drugs and analgesics could effectively alleviate symptoms from ketamine cystitis. However, abstinence from ketamine usage and the amount of ketamine consumed remained two important factors concerning the response to treatment as well as symptom relief.

題目：前瞻性縱貫研究氯胺酮誘發排尿功能障礙患者在標準化治療方案下各種不同治療的療效 (BDF110010)

報告摘要

引言：

由於在世界各地誤以氯胺酮為消遣使用的增長，氯胺酮引致排尿功能障礙已成為一個嚴重的醫療問題。雖然，病情的臨床表現逐漸清晰，但基本的病理生理學仍然所知甚少。此外，目前的治療大部分只基於小數臨床報告系列的經驗，現有的文獻中，並沒有較大型的患者樣本或標準治療的建議。由於患者正在急劇增加，這實在有需要透過臨床研究驗證有關的治療方案，以向患者提供更有效的實證為本治療。因此，我們進行了一項前瞻性研究，觀察在一個標準化治療方案下，各種不同治療的成效。我們希望此研究能幫助評估各種治療氯胺酮引致排尿功能障礙的療效及接受程度。

方法：

這項前瞻性病例組別包括了所有曾在我們中心接受治療的氯胺酮引致排尿功能障礙患者。患者的標準治療方案可分為四個不同級別：第一線治療包括抗發炎藥物 / 抗毒蕈鹼劑，第二線治療包括阿片類鎮痛藥 / 普瑞巴林，第三線治療包括膀胱腔內灌注透明質酸治療，及第四線手術治療包括膀胱水擴張及膀胱擴大手術。我們用徵狀分數（PUF），生活質素健康問卷 (EuroQol)，總體反應評估 (GRA) 及尿速測試來評估治療效果。我們也會記錄在治療中出現的任何不良反應。同時，我們會評估可以影響治療效果的預測因素。

結果：

在 2011 年 12 月至 2014 年 6 月期間，共有 463 名患者在我們的中心接受治療，其中 294 名患者是在本計劃期間 (2012 年 7 月至 2014 年 6 月) 第一次到我們的中心接受評估。醫療團隊會根據一個標準化的治療方案向所有患者提供治療。319 名患者有持續覆診並接受跟進評估，其中 126 名患者的跟進時間超過 1 年，整體平均跟進時間為 10.7 ± 8.5 個月。在接受第一線治療後及有覆診最少一次的 290 名患者中，202 (69.7%)名患者報告徵狀有改善，46 (15.9%)名患者報告徵狀相若及 42 (14.5%)名患者報告徵狀比之前差。患者在接受第一線治療後的徵狀分數，生活質素分數及排尿量都顯著地改善。同時，每星期氯胺酮使用量及持續停用氯胺酮都是預測改善徵狀分數的顯著因素。62 名需要接受第二線治療的患者中 42 (67.7%) 名患者報告徵狀有改善。同時，徵狀分數、生活質素分數及排尿量都有顯著改善。每星期氯胺酮使用量及持續停用氯胺酮及基線徵狀分數都是預測患者需要接受第二線治療的顯著因素。8 名病人完成膀胱腔內灌注透明質酸療程，他們在接受療程後的排尿量有顯著改善，其中 5 名病人減少使用口服藥物。患者在接受第一線治療後，發現共有 109 個患者有不良反應，大部份報告的不良反應都是輕微的，主要與服用抗毒蕈鹼劑有關。患者在接受第二線及第三線治療後，沒有報告不良反應。

總結：

本臨床報告驗證了用標準化治療方案治療氯胺酮引致排尿功能障礙的成效。抗發炎藥物及鎮痛藥都可以有效地舒緩氯胺酮引致的膀胱炎。但是，持續停用氯胺酮及過去氯胺酮使用量仍然是影響治療成效及減輕徵狀的兩個重要因素。

Introduction

Ketamine, being a receptor complex antagonist N-methyl-D-aspartic acid, has been used for anesthetic and analgesic purposes since 1960s[1]. Its recreational use was subsequently reported in 1970s, and has become increasingly common in the past 20 years[2]. 0.8% of individuals aged 16 to 24 years were reported to be using ketamine per year in United Kingdom[3], and it has been the commonest abusive substance in teenagers since 2005 in our locality[4].

Urinary tract symptoms were reported in over a quarter of regular ketamine users[5]. With long-term ketamine exposure, pathology of the urinary tract including detrusor overactivity, diminished bladder compliance, vesico-ureteric reflux and ureteric obstruction were observed[6]. While many recognized that abstinence from ketamine is by far the most effective treatment option[7], oral or intravesical medication, as well as surgical intervention, have been attempted to alleviate the detrimental impact brought along by ketamine abuse on the genitourinary system[8]. We have previously reported a cross-sectional study on symptoms and voiding parameters of patients from a dedicated centre treating ketamine-associated uropathy[9]. In this prospective cohort of patients, different tiers of intervention were adopted, ranging from oral medication to more invasive modalities. After more than 2 years of medical care for this group of patients, we report here on our experience of ketamine-associated uropathy management and the outcome of intervention.

Methods

Since December 2011, all consecutive patients who attended our centre for ketamine related urological problems were seen in a dedicated clinic, and were recruited into a prospective cohort with standardized treatment regime. Written informed consent was given by all participants prior to entering the study.

Basic demographic data were recorded before clinic attendance. Upon the first consultation, serum creatinine level, urine microscopy and culture and uroflowmetry were performed. Functional bladder capacity (FBC) was calculated by adding the voided volume to post-void urine residuals during uroflowmetry assessment. Symptom assessment was done by means of the pelvic pain and urgency/frequency symptom scale (PUF symptom score) and EuroQol Visual Analogue Scale (EQ VAS). The Chinese version of the PUF symptom score is a validated assessment tool for cystitis[10], and EQ VAS is a 0-100 visual scale for patient's subjective assessment of his or her own health state. The higher the score, the better the patients perceive their health state. Ultrasound of the urinary system was done to look for any sign of obstructive uropathy.

As abstinence is the key to successful symptom relief, all patients who attended the clinic were offered motivational interview, patient education and social worker support. Medical treatment for ketamine-associated urological problems were divided into multiple tiers. First-line treatment included non-steroidal anti-inflammatory drug (NSAID) e.g. Diclofenac and Etoricoxib, and anti-cholinergic agents e.g. Solifenacin. Phenazopyridine and paracetamol were used for pain control. If first-line treatment could not provide sufficient symptom relief, opioid group of analgesics e.g. Tramadol, and pregabalin were added. Further treatment with a course of intravesical instillation of sodium hyaluronate was offered if symptom control was still suboptimal after second-line treatment. Surgical intervention, e.g. augmentation cystoplasty and hydrodistension, was performed if indicated.

Patients were followed-up on a regular basis, depending on symptom severity as well as other social factors, with reassessment of uroflowmetry, PUF symptom score and EQ VAS. Ketamine abuse status was reviewed, and treatment response was evaluated.

Descriptive statistics were used to characterize the clinical characteristics of the study cohort. Abstinence was defined as abstaining from ketamine use for at least 4 weeks. T-test and one way ANOVA test were used for continuous data, and Mann-Whitney U test and Kruskal Wallis Test were used for skewed data. Chi-square test or trend test was applied for categorical data. The pre and post treatment effect was tested with paired T-test and Wilcoxon signed-rank test. All post-hoc tests for multiple comparison were performed with Bonferroni adjustment. Univariable and multivariable logistic regression analyses were performed to identify clinical covariates that were significantly associated with clinical outcome. *P* values <0.05 were considered statistically significant. SPSS software package version 21 (SPSS Inc, Chicago, IL, USA) was used for all calculations.

Results

Between December 2011 and June 2014, 463 patients attended our clinic for KIVD, with 294 of them were first assessed during the project period, and all were managed by the same team with the same standardized protocol. There was slightly more ladies in our cohort (258 patients; 55.7%) and the mean age was 25.0 ± 3.8 years old. After their first consultation, 319 patients came back for follow-up assessment (default rate 31.1%), with an overall mean follow-up of 10.7 ± 8.5 months, and 126 patients have more than 1-year follow-up data available for review. (Table 1) Among these, 101 patients were already abstinent before their first consultation, and 218 patients were active ketamine users. There was no significant difference between these 2 groups of patients in terms of gender composition and mean age. For the baseline parameters, mean PUF total score was significantly higher (23.3 ± 6.7 Vs 19.8 ±7.7, $P<0.0005$), and EQ VAS was significantly worse (49.5 ± 21.1 Vs 62.5 ± 22.3, $p=0.001$) in the active ketamine user group. Mean functional bladder capacity in the abstinent group was 177.8 ± 122.9 ml, and that in the active ketamine user group was 125.2 ± 116.4 ml, $p=0.001$.

Upon the last follow-up during the study period, 23 patients were not on any treatment and 290 patients had used first-line treatment. Among these 290 patients, 56 of them were required to escalate the treatment to second-line at some time point during the study period. Six patients were started on second line therapy during their first consultation, as they were already on our first line therapy prior to our consultation. Therefore, there were altogether 62 patients who required second line therapy in our cohort. (Table 2) Seventeen patients received intravesical therapy. Two patients had surgical intervention done during the project period.

Both first-line and second-line treatments were found to be effective in improving PUF score, EQ VAS and functional bladder capacity. (Table 2 and Table 3) In order to assess the effect of ketamine abstinence on treatment outcome, patients were subdivided into 3 groups. Group 1 were patients who had been

abstinent before attending our clinic. Group 2 were patients who became abstinent after attending our clinic. Group 3 were patients still being active ketamine users at the last follow-up during the study period. We found that for all three groups, intervention with first-line or second-line treatment were effective in achieving significant improvement in PUF score, EQ VAS, general response assessment (GRA) and FBC. For both first and second line treatment, Group 2 had better improvement compared to Group 3, and this suggested abstinence combining with medical treatment yielded better result than medical treatment alone.

Age, gender, smoking history, availability of social worker support, amount of ketamine consumed per week, duration of ketamine abuse, coingestion, abstinence status, PUF score, EQ VAS and FBC were analysed using logistic regression to predict first-line treatment failure (Table 4). All the baseline clinical outcomes, baseline PUF score, EQ VAS score and FBC were found to be significant predictive factors on univariable analysis. Therefore, multivariable analyses were done to look at the effect of these individual clinical areas on predicting first-line treatment failure together with the other factors. The amount of ketamine consumed, abstinence status, baseline PUF score, EQ VAS score and FBC were found to be significant predictive factors on multivariable analysis.

Another multivariable analysis was performed to look for predictors for an improvement of PUF total score more than 25%. Factors that were taken into consideration included age, gender, baseline abstinence status, availability of social worker support, smoking status amount of ketamine consumed per week, and duration of ketamine abuse. Again, amount of ketamine consumed per week (adjusted OR 0.769, 95%CI 0.624 – 0.949, p-value=0.014) and abstinence status of patients (adjusted OR 2.373, 95%CI 1.413 – 3.985, p-value=0.001) were found to be the significant predictor of improvement of PUF total score.

In our cohort, we had 17 patients who underwent intravesical sodium hyaluronate, with 8 of them completed the treatment. Besides there was a

significant improvement in voided volume for the patients after treatment, 5 of them could step down their oral medication usage. (Table 5)

One patient went for hydrodistension, and another patient went for robotic-assisted laparoscopic augmentation cystoplasty. Both procedures were completed without complication. However, for the lady who had received hydrodistension, her symptoms recurred soon after the procedure. There was also one patient pending for augmentation cystoplasty.

Amongst the 319 patients with at least one follow-up, 109 adverse effects were reported. All were related to the first line therapy. Most of them were mild and related to the use of anticholinergic agents. (Table 6) No adverse effect was reported after second and third line treatment.

Discussion

Since the initial case series of ketamine cystitis reported by Shahani *et al*[11] and Chu *et al*[6] in 2007, this unique disease entity has been gaining an increasing recognition. Investigators from various countries have reported their clinical observation in this aspect[12,13]. Typical features of lower urinary tract symptoms (LUTS) after prolonged ketamine abuse include dysuria, painful haematuria, urinary urgency, urge incontinence, frequency and nocturia[14]. In our series, the mean FBC of our patients was 141.8 ± 120.8 ml (Table 1). This is significantly smaller than the reported FBC in a normal population[15], which would partly account for the storage symptoms experienced by patients with ketamine cystitis. Furthermore, the dysuria symptoms and LUTS of ketamine cystitis were reflected in our study by the mean PUF total score of 22.2 ± 7.2 (Table 1), which was significantly higher when compared with normal subjects with a negative history of ketamine abuse (mean PUF total score: 2.1 ± 2.4; mean PUF symptom score: 1.6 ± 1.5; mean PUF bother score 0.6 ± 2.0)[16].

Abstaining from ketamine abuse is regarded as the milestone of treating KIVD [16], and with abstinence symptom resolution has been observed[5,17]. From our data concerning the symptom severity upon first consultation, while both the abstinent group and active ketamine user group had similar duration of ketamine abuse, the PUF score, EQ VAS and FBC were significantly worse than that of the active user group (Table 1). Furthermore, for those patients who received either first or second line therapy, the improvement in symptoms and voiding volume were much better if the patients were abstinence from ketamine. (Table 2 & 3) These findings would be evidences to support cessation of ketamine abuse being an important management strategy to tackle ketamine-associated uropathy.

However, breaking the habit of ketamine abuse is not easy. In our series, only 96 patients out of the 218 active ketamine users managed to attain an abstinence state during the study period. Furthermore, certain degree of LUTS persisted after abstinence (Table 1). Thus, there is a need to find strategies to relieve the

symptoms from ketamine cystitis besides advocating abstinence to patients. According to the bladder biopsy histology reported in the literature of ketamine cystitis, there is a strong component of inflammation in this disease entity. Shahani *et al* found scattered lymphocytes and mast cells throughout the stroma with predominating eosinophils, mimicking the changes of chronic cystitis[11]. Chen *et al* found neutrophilic and lymphoplasma cell infiltration in bladder mucosa, which was consistent with chronic inflammation[13]. In a rat urinary bladder model, an up-regulations of cyclooxygenase-2 (COX2) expression was noted[18]. Such findings supported our use of anti-inflammatory drug in our first-line treatment for ketamine cystitis. With the use of our first-line treatment, there was a statistically significant improvement in both PUF score and FBC (Table 2). Almost 70% of patients subjectively felt the treatment had improved their condition on GRA. Furthermore, from our multivariate analysis patients with less ketamine consumption per week had a better response to first-line treatment. This implies that the outcome of treatment does not only depend on abstinence state. A history of heavy ketamine abuse would have sequelae on future treatment response, even if the patient finally manages to achieve an abstinence state.

In our series, about 20% of patients were required to step up to second-line treatment after the initial course of first-line treatment (Table 3). In our initial experience of managing ketamine cystitis, anti-depressant e.g. amitriptyline was considered part of the second-line treatment because it was believed to counter LUTS to some extent[19]. However, as most patients failing first-line treatment were due to persistent pelvic pain or dysuria, more potent analgesics were used in the second-line treatment. This provided a significant improvement in PUF score and EQ VAS, demonstrating the usefulness of opioid analgesic and pregabalin type of medication in a selected group of patients.

In a study by Gu *et al*, they investigated the effect of ketamine on bladder using a rat model[20]. It was found that ketamine or its urinary metabolites disrupted the proliferation of bladder epithelial cells, resulting in defected bladder epithelial barrier. Subsequent leakage of urinary potassium caused a stress response in the

bladder and provoked cystitis. Hyaluronic acid is a natural proteoglycan that repairs defects in the glycosaminoglycan (GAG) layer. Intravesical administration of this medication was employed in the treatment of interstitial cystitis / bladder pain syndrome with success[21]. Furthermore, previous study suggested its use would reduce analgesic consumption in patients with ketamine cystitis[22]. Thus we administered intravesical hyaluronic acid as one of the treatment options for ketamine cystitis. From the results of the 8 patients completed intravesical treatment, there was a significant improvement in voided volume for the patients after treatment. Five of them could step down their oral medication usage. (Table 5) Our results supported the use of this intravesical therapy in patients with intractable pain despite potent analgesics.

Currently there are a few questionnaires available for the evaluation of patients with chronic pelvic pain syndrome (CPPS). However, when the most used questionnaires for quality of life (QoL) assessment in patients with CPPS were compared, very different results could be found, indicating that results from one questionnaire cannot be used for overall conclusions concerning pain intensity and QoL[23]. To improve the assessment accuracy, we have employed multiple assessment tools to measure the outcome of treatment, including PUF symptom score, EQ VAS and GRA. Furthermore, the Chinese version of the PUF questionnaire was shown to be a reliable and valid tool to assess LUTS in patients with ketamine cystitis[16]. Thus the outcome of our intervention can be evaluated with better confidence and precision.

Limitation of our study stemmed from the relatively poor compliance of our patients to treatment scheme. In an ideal situation, regular follow-up of the patients could allow better assessment of treatment response and treatment tolerance, thus making adjustment of intervention more rapid. However, our series demonstrated a high default rate among our patients, which could be reflected by the fact that only 319 patients out of a total of 463 patients turned up for follow-up after first consultation. With a poorer compliance to treatment, the actual benefit of intervention might have been underestimated.

In our initial proposed treatment protocol, the proposed treatment protocol was: First line treatment - Oral non-steroidal anti-inflammatory drugs (or COX II inhibitor) & anticholinergic agents; Second line treatment: for pain control – additional treatment of amitriptyline, followed by gabapentin; Third line treatment - a course of intravesical hyaluronate therapy; Fourth line treatment - intradetrusor injection of botulinum toxin and Fifth line treatment – surgical intervention. However, with the cumulating clinical experience, from our and other colleagues' observation, as well as patients' feedback, we have made some minor modification in our protocol. While the first line treatment remains the same, the second-line involves mainly the use of more potent analgesics, including tramadol and also gabapentin / pregabalin. This modification was in response to the fact that intractable pain and dysuria were the main reasons for failing first line treatment among these patients. Furthermore, the initial proposal to use botulinum toxin injection after failing intravesical hyaluronate instillation was withheld. This was based on our current understanding that the decrease in bladder capacity in these patients is more related to tissue fibrosis rather than detrusor overactivity. As a result, we decided that the treatment of botulinum toxin injection was not an appropriate option for these patients. These minor modifications in the treatment protocol on the way of our study reflected that the management of KIVD is not yet optimal and the scientific community is still in the process of finding a better solution for treatment. We hope our project could fill in the current knowledge gap in the area of KIVD management.

Moreover, in our initial plan, patients would be followed-up regularly to assess treatment response. However, in real life practice, there are many factors that can affect the compliance to the scheme. These parameters include the compliance of patients to follow-up, proximity of their rehabilitation hostel to our centre, as well as if the patient is under custody of Hong Kong Correctional Services. Therefore, while we tried to see the patients regularly as we had proposed, we also made some adjustments in the follow-up arrangement in order to improve the patient's compliance to our management. Furthermore, our staff would take the initiative to contact those defaulted patients for re-arranging

follow-up if they have missed the designated appointment. As a result, the follow-up schedule had some variations compared to the initial plan. Again, this reflects the difficulty in real life clinical practice and also the challenge in the management of patients with KIVD.

Besides oral and intravesical medication, surgical management of ketamine cystitis has been reported in the literature[8,24]. Both hydrodistension[25] and augmentation cystoplasty[8] were demonstrated to be effective in selected patients. In our series, we had stringent criteria to select patients into surgical management, that is significant symptoms failing non-invasive treatment with more than a 6-month history of abstaining from ketamine abuse. Together with the reluctance from some patients to undergo invasive therapy, this may explain the scanty number of patients who underwent surgical intervention for ketamine cystitis in our series. However, ketamine abuse is more than a medical problem. It is also a social problem. Ensuring good compliance from patients as well as exhausting non-invasive means of symptom relief seem to be a reasonable approach before embarking on more invasive surgical options for managing ketamine-associated uropathy. Further study is needed to look for more effective intervention, as well as looking for ways to minimize the prevalence of ketamine abuse in the first place.

Conclusion

Ketamine abuse produced significant LUTS and pain, which were more severe in active users than ex-users. This is a prospective case series demonstrating the efficacy of managing ketamine-associated uropathy using a four-tier approach. Both NSAID and analgesics could effectively alleviate symptoms from ketamine cystitis. Abstinence from ketamine usage as well as the amount of ketamine consumed have bearings on treatment response and symptom relief. Further study is needed to evaluate the efficacy of intravesical treatment and surgical intervention.

Conflicts of Interest

None of the contributing authors have any conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Table 1. ***Baseline demographics and characteristics for patients with at least one follow-up***

	Overall	Abstinence*	Active User**	*p*-value
Subjects (n)	319	101	218	
Gender				
Male	132 (41.4%)	41 (40.6%)	91 (41.7%)	0.846
Female	187 (58.6%)	60 (59.4%)	127 (58.3%)	
Mean age, years ± SD	25.1 ± 3.6	24.9 ± 3.9	25.2 ± 3.5	0.464
Mean FU, months ± SD	10.7 ± 8.5	8.0 ± 6.5	12.0 ± 9.0	<0.0005
Frequency of ketamine use[#]				
<1 time / week	10 (4.6%)	--	10 (4.6%)	--
1-3 times / week	33 (15.1%)		33 (15.1%)	
4-6 times / week	22 (10.1%)		22 (10.1%)	
≥7 times / week	153 (70.2%)		153 (70.2%)	
Ketamine consumed / week, gram ± SD	15.7 ± 12.0	--	15.7 ± 12.0	--
Duration of ketamine abuse, months ± SD	82.3 ± 35.9	78.7 ± 34.4[##]	83.9 ± 36.6	0.226
PUF total score ± SD	22.2 ± 7.2	19.8 ± 7.7	23.3 ± 6.7	<0.0005
Symptom score ± SD	14.0 ± 4.7	12.4 ± 5.0	14.8 ± 4.3	<0.0005
Bother score ± SD	8.2 ± 2.9	7.4 ± 3.1	8.6 ± 2.7	0.001
EQ VAS ± SD	53.3 ± 22.2	62.5 ± 22.3	49.5 ± 21.1	0.001
FBC, ml ± SD	141.8 ± 120.8	177.8 ± 122.9	125.2 ± 116.4	0.001

*Abstinence was defined as abstaining from ketamine use for 4 weeks prior to first consultation.

**Active user of ketamine upon first consultation.

[#]Frequency of ketamine use upon first consultation

[##]Duration of ketamine abuse before abstinence

Abbreviations: SD = Standard deviation; FU = Follow-up; PUF = Pelvic pain and urgency/frequency; EQ VAS = EuroQol Group visual analogue scale; FBC = Functional bladder capacity

p-value signifies the difference between abstinence group and active ketamine user group.

Table 2. *Subjects characteristics with first-line treatment*

	Overall	Group 1	Group 2	Group 3	*p*-value
Subjects (n)	290	83	96	111	
Gender					
Male	120 (41.3%)	33 (39.8%)	44 (45.8%)	43 (38.7%)	0.550
Female	170 (58.6%)	50 (60.2%)	52 (54.2%)	68 (61.3%)	
Mean age, years ± SD	25.1 ± 3.7	24.9 ± 4.0	24.8 ± 3.9	25.6 ± 3.2	0.312
Mean FU, months ± SD	9.3 ± 7.8	7.0 ± 5.8	11.8 ± 8.0	8.8 ± 8.3	<0.0005
Frequency of ketamine use[#]					
Abstinence*	83 (28.6%)	--	0	0	
<1 time / week	10 (3.4%)		6 (6.3%)	4 (3.6%)	
1-3 times / week	21 (7.2%)		12 (12.5%)	18 (16.2%)	
4-6 times / week	30 (10.3%)		12 (12.5%)	9 (8.1%)	
≥7 times / week	146 (50.3%)		66 (68.8%)	80 (72.1%)	0.513[&]
Ketamine consumed / week, gram ± SD[#]	15.4 ± 12.1	--	15.2 ± 10.7	15.6 ± 13.2	0.840[&]
Duration of ketamine abuse, months ± SD[##]	83.4 ± 36.5	81.0 ± 35.2	79.3 ± 36.4	88.6 ± 37.2	0.151
Requiring 2nd line treatment	56 (19.3%)	13 (15.7%)	14 (14.6%)	29 (26.6%)	0.067

	Pre	Post[&&]	Pre	Post[&&]	Pre	Post[&&]	Pre	Post[&&]	
PUF total score ± SD	22.8±6.7	16.7±8.5	21.1±6.6	14.8±7.6	24.0±6.9	14.6±8.4	23.1±6.4	20.0±8.3	<0.0005
Symptom score ± SD	14.4±4.3	10.7±5.3	13.2±4.3	9.6±4.8	15.2±4.4	9.4±5.4	14.6±4.2	12.6±5.2	<0.0005
Bother score ± SD	8.4±2.7	6.0±3.4	7.9±2.7	5.1±3.1	8.8±2.8	5.3±3.3	8.6±2.6	7.4±3.4	<0.0005
EQ VAS ± SD	52.6±22.0	63.4±21.1	60.0±22.2	68.63±20.6	48.8±2.2	67.3±22.2	50.6±20.7	56.3±18.9	<0.0005
GRA									<0.0005
Improved	--	202(69.7%)	--	61(73.5%)	--	83(86.5%)	--	58(52.3%)	
Unchanged		46(15.9%)		15(18.1%)		7(7.3%)		24(21.6%)	
Worsen		42(14.5%)		7(8.4%)		6(6.3%)		29(26.1%)	
FBC, ml ± SD	133.5±110.5	157.8±122.2	169.7±121.4	178.7±128.4	109.9±97.7	193.4±128.5	127.0±106.5	111.5±95.4	<0.0005

Group 1: Already abstinence before attending clinic; Group 2: Became abstinence after attending clinic; Group 3: Still active ketamine user at latest follow-up

*Abstinence was defined as abstaining from ketamine use for 4 weeks prior to first consultation.

[#]Frequency or amount of ketamine use upon first consultation

[##]Duration of ketamine abuse before abstinence

[&]Group 2 Vs Group 3 only

[&&]Data of the latest follow-up with 1st line treatment

Abbreviations: SD = Standard deviation; FU = Follow-up; PUF = Pelvic pain and urgency/frequency; EQ VAS = EuroQol Group visual analogue scale; GRA = General Response Assessment; FBC = Functional bladder capacity; Pre = Pre-treatment; Post = Post-treatment

Table 3. *Subjects characteristics with second-line treatment*

	Overall	Group 1	Group 2	Group 3	*p*-value
Subjects (n)	62	17	34	11	
Gender					
Male	25 (40.3%)	7 (37.5%)	14 (41.2%)	5 (45.5%)	0.550
Female	37 (59.7%)	10 (62.5%)	20 (58.8%)	6 (54.5%)	
Mean age, years ± SD	26.1 ± 4.0	24.9 ± 4.0	24.8 ± 3.9	25.6 ± 3.2	0.312
Mean FU, months ± SD	15.3 ± 10.0	10.5 ± 7.3	17.8 ± 10.2	15.2 ± 10.3	0.043
Frequency of ketamine use[#]					
Abstinence*	17 (27.4%)	--	0	0	
<1 time / week	2 (3.2%)		2 (5.9%)	0	
1-3 times / week	5 (8.1%)		4 (11.8%)	1 (9.1%)	
4-6 times / week	5 (8.1%)		5 (14.7%)	0	
≥7 times / week	33 (53.2%)		23 (67.6%)	10 (90.9%)	0.211[&]
Ketamine consumed / week, gram ± SD[#]	18.2 ± 16.2	--	17.4 ± 11.5	20.6 ± 26.4	0.672[&]
Duration of ketamine abuse, months ± SD[##]	86.7 ± 36.1	87.8 ± 28.0	92.7 ± 39.5	67.8 ± 30.9	0.151

	Pre[&&]	Post	Pre[&&]	Post	Pre[&&]	Post	Pre[&&]	Post	
PUF total score ± SD	24.9±6.7	18.1±6.6	22.5.±8.1	18.5±8.1	25.4±6.8	17.9±6.4	19.8±5.9	18.4±5.0	<0.0005
Symptom score ± SD	15.6±4.5	11.6±4.1	14.1±5.1	11.6±5.1	16.1±4.4	11.6±4.0	12.2±3.1	11.5±2.8	<0.0005
Bother score ± SD	9.2±2.6	6.5±2.8	8.4±3.4	6.8±3.3	9.3±2.7	6.3±2.7	7.5±2.9	6.8±2.4	<0.0005
EQ VAS ± SD	46.1±25.1	62.0±17.7	62.1±24.4	64.8±21.3	43.5±18.2	62.8±16.3	59.8±14.0	57.5±13.6	0.015
GRA									
Improved	29(51.8%)	42(67.7%)							0.165
Unchanged	10(17.9%)	10(16.1%)							
Worsen	17(30.4%)	10(16.1%)							
FBC, ml ± SD	101.8±82.6	114.7±97.7	131.1±99.5	143.7±71.8	75.7±58.8	104.0±107.1	104.4±80.7	105.6±99.4	0.030

Group 1: Already abstinence before attending clinic; Group 2: Became abstinence after attending clinic; Group 3: Still active ketamine user at latest follow-up

*Abstinence was defined as abstaining from ketamine use for 4 weeks prior to first consultation.

[#]Frequency of ketamine use upon first consultation

[##]Duration of ketamine abuse before abstinence

[&]Group 2 Vs Group 3only

[&&]Data just before the start of 2nd line treatment

Abbreviations: SD = Standard deviation; FU = Follow-up; PUF = Pelvic pain and urgency/frequency; EQ VAS = EuroQol Group visual analogue scale; GRA = General Response Assessment; FBC = Functional bladder capacity; Pre = Pre-treatment; Post = Post-treatment

Table 4. ***Factors predicting the need for second line therapy after first line therapy***

	Univariable				Multivariable			
	OR [95%CI]	*p*-value	Adjusted OR [95%CI]	*p*-value	Adjusted OR [95%CI]	*p*-value	Adjusted OR [95%CI]	*p*-value
Age	1.082 [1.005 – 1.164]	0.036	--		--		--	
Gender(Female)	0.947 [0.547 – 1.640]	0.847	--		--		--	
Social worker support	0.969 [0.537 – 1.749]	0.917	--		--		--	
Coingestion	0.951 [0.553 – 1.636]	0.856	--		--		--	
Smoking	0.837 [0.399 – 1.755]	0.637	--		--		--	
Amount of ketamine consumed	1.021 [1.005 – 1.036]	0.008	1.024 [1.007 – 1.041]	0.004	1.028 [1.011 – 1.045]	0.001	1.020 [1.004 – 1.037]	0.013
Duration of ketamine abuse	1.003 [0.995 – 1.010]	0.513	--		--		--	
Abstinence from ketamine	0.618 [0.357 – 1.071]	0.086	0.539 [0.296 – 0.982]	0.043	0.534 [0.293 – 0.973]	0.041	--	
Baseline PUF total score	1.076 [1.031 – 1.123]	0.001	1.069 [1.022 – 1.117]	0.003				
Baseline PUF symptom score	1.112 [1.043 – 1.185]	0.001						
Baseline PUF bother score	1.193 [1.070 – 1.330]	0.002						
Voided volume (ml)	0.996 [0.992 – 0.999]	0.018						
FBC (ml)	0.996 [0.993 – 0.999]	0.009			0.996 [0.993 – 0.999]	0.010		
EQ VAS	0.984 [0.972 – 0.997]	0.015					0.983 [0.970 – 0.997]	0.015

Abbreviations: OR = odd ratio; PUF = Pelvic pain and urgency/frequency; EQ VAS = EuroQol Group visual analogue scale; FBC = Functional bladder capacity

Table 5. ***Subjects characteristics with third-line treatment***

	Intravesical Sodium Hyaluronate		*p*-value
Subjects (n)	17		
Gender			
Male	7 (41.2%)		
Female	10 (58.8%)		
Mean age, years ± SD	26.0 ± 5.8		
Mean FU, months ± SD	13.9 ± 9.0		
Frequency of ketamine use[#]			
Abstinence*	9 (52.9%)		
<1 time / week	1 (5.9%)		
1-3 times / week	0		
4-6 times / week	3 (17.6%)		
≥7 times / week	5 (29.4%)		
Ketamine consumed / week, gram ± SD[#]	16.6 ± 10.3		
Duration of ketamine abuse, months ± SD[##]	82.6 ± 37.0		
	Pre[&]	Post	
PUF total score ± SD	23.0 ± 6.8	22.4 ± 8.9	0.657
Symptom score ± SD	14.4 ± 4.4	14.6 ± 5.8	0.906
Bother score ± SD	8.5 ± 2.7	7.8 ± 3.3	0.111
EQ VAS ± SD	50.0 ± 24.3	48.1 ± 23.1	0.476
VV	57.3 ± 36.0	77.9 ± 44.8	0.039
PVR	11.6 ± 21.2	9.25 ± 20.2	0.465
FBC	68.9 ± 39.6	87.1 ± 42.5	0.131
VV/FBC	85.9 ± 23.0	89.6 ± 20.0	0.465

Group 1: Already abstinence before attending clinic; Group 2: Became abstinence after attending clinic; Group 3: Still active ketamine user at latest follow-up

*Abstinence was defined as abstaining from ketamine use for 4 weeks prior to first consultation.

[#]Frequency or amount of ketamine use upon first consultation

[##]Duration of ketamine abuse before abstinence

[&]Data just before the start of 3rd line treatment

Abbreviations: SD = Standard deviation; FU = Follow-up; PUF = Pelvic pain and urgency/frequency; EQ VAS = EuroQol Group visual analogue scale; VV = Voided volume; PVR = Post-void residual; FBC = Functional bladder capacity; Pre = Pre-treatment; Post = Post-treatment

Table 6. ***Adverse events after treatment***

Subjects (n)	290*
Number of subjects experience adverse events	109 (37.6%)
Difficulty in passing urine	50 (17.2%)
Dry mouth	29 (10.0%)
Dry eyes	3 (1.0%)
Constipation	31 (10.7%)
Epigastric pain	15 (5.2%)
Pain after voltaren	7 (2.4%)
Pain after pyridium	11 (3.8%)
Pelvic pain after drugs	2 (0.7%)
Others**	6 (2.1%)

*Number of patients received first line treatment

**Others – increased hand tremor, increased mucus in urine, bilateral ankles and joint pain, throat discomfort, sleepiness

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