Title page

A Multicentre, Prospective, Randomized, Double-Blind Study To Measure the Treatment effectiveness of Abobotulinum A (BTXA) among Women with Refractory interstitial cystitis/bladder pain syndrome.

Authors and affiliations

Dr J Manning(Corresponding Author); John Hunter Hospital, NSW Australia

PO Box 648 The Junction 2291 NSW Australia

Phone; 61 02 49408069

Fax; 61 02 49610599

Jma14246@bigpond.net.au

Prof Peter Dwyer;Mercy Hospital for Women, Vic, Australia

Adj Assoc Prof Anna Rosamilia; Monash Medical Centre, Vic, Australia

Kim Colyvas; University of Newcastle, NSW, Australia

Christine Murray RN; Mercy Hospital for Women, Vic, Australia

Elizabeth Fitzgerald; RN; Monash Medical Centre, Vic, Australia

Conflict of Interest; PD is on Advisory Board for Allergan

Contribution to Authorship

Manning J; Conceived study design, made ethics applications and extensions, arranged assistance with funding, enrolled patients at 1 site, collated all data, analysed results with assistance from K Colyvas (statistical support), wrote paper

Prof Dwyer P; enrolled ½ of subjects, reviewed paper

Thomas E; RN CNS; collated data, involved in treating subjects

Murray C; RN CNS; collated data, involved in treating subjects

Rosamilia A; enrolled subjects, very extensively reviewed drafts of paper

Abstract

Introduction;

To determine if Abobotulinumtoxin A (AboBTXA) is an effective treatment for Interstitial Cystitis/Bladder Pain Syndrome.

Methods;

54 women with severe, refractory IC were randomised from 3 referral centres.

Double blind design with random allocation to treatment with hydrodistension and injection of normal saline, or hydrodistension and injection of AboBTXA.

Main Outcome measures;

The O'Leary Sant questionnaire consists of the problem (OLS PI) and symptom index (OLS PI) scores and the bladder diary data were compared between AboBTXA and control subjects at baseline and at 3 month follow-up. Measurements were made beyond 3 months, but no further randomized comparison was possible due to the ability of non responsive patients in either group to have AboBTX treatment.

Results;

Complete data was available in 50 subjects and in both groups, the OLS questionnaires showed improvement at 3 months. Only the OLS PI was improved in the BTXA group (p=0.04). At 3 months, no difference was found in the OLS SI or the total OLS score. Twelve subjects had UTI treated during the follow-up period which confounded the results. In the 38 subjects without UTI there was improvement in the total OLS score (p=0.02), the OLS PI (0.08) and the OLS SI (p=0.008) for the Abo BTXA group at 3 months. Only 5 AboBTXA compared with 2 control subjects had a 50% reduction of their OLS score.

Conclusions

For chronic refractory IC/BPS patients, AboBTXA was associated with no overall improvement in total OLS score although significant benefit was noted in a small number of patients. The absence of post treatment UTI was associated with a better response to AboBTXA.

f. Keywords

Abobotulinum toxin, Botulinum toxin A, Hydrodistension, Interstitial cystitis, Prospective, Bladder pain syndrome

Brief Summary

AboBotulinum toxin was not shown to be effective for the treatment of refractory interstitial cystitis.

Abbreviations

OnaBTXA- onabotulinumA toxin (Botox®)

AboBTXA- abobotulinumA toxin (Dysport®)

UTI- urinary tract infection

IC/BPS interstitial cystitis bladder pain syndrome

OLS - O'Leary Sant questionnaire score

BCG- BacilleCalmette Guerin

Introduction

Preliminary evidence suggested that Botulinum toxin A (BTXA) may be effective for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) when injected into the bladder wall (1-5).

In 2005, El-Bahnasy et al reported results of a prospective study of 36 women with refractory IC/PBS randomised to have either BCG weekly for 5 weeks, or injection of 300 U of Onabotulinumtoxin (Botox®). Significant improvement was noted in the domains of daytime frequency, nocturia, pelvic pain, urgency and dysuria among women randomized to treatment with BTXA . No significant difference in complications between groups, in particular voiding dysfunction, was noted (6).

Several mechanisms for the possible effectiveness of BTXA in the treatment of bladder pain have been suggested. BTXA may inhibit the release of neuropeptides such as Substance P, calcitonin gene related peptide and glutamate which are all involved in pain transmission from either dorsal root ganglion neurones, sensory afferent nerves, and/ or urothelial cells. It is speculated that this could happen in a similar way to that in which BTXA inhibits acetylcholine release from motor nerve terminals by cleavage of snap proteins.

The aim of this study was to determine using a prospective randomised double blind design, whether hydrodistension with injection of BTXA into the bladder wall could significantly improve symptoms for women with chronic refractory IC/BPS when compared to treatment with hydrodistension and saline injection

Materials and Methods

From January 2004 until February 2009, 54 female subjects with longstanding, refractory IC/PBS were recruited from urogynecology clinics at 3 centres. They were followed up for at least a further 2 years. Subjects all met the NIDDK (7) criteria in use at that time, with the majority having had multiple prior therapies. Refractory was defined as those who had failed 2 or more recognized treatments. Subjects were over 18 years of age. Exclusion criteria included a known history of recurrent urinary tract infection (UTI), current pregnancy, bladder malignancy, steroid use, and voiding difficulty. All subjects completed a three day bladder diary and baseline questionnaires. The primary outcome measure was the O'Leary Sant questionnaire score (OLS) which is composed of 2 parts; the OLS Symptom Index (OLS SI) and the OLS Problem index (OLS PI); the latter is similar to a bother score;"how much has this been a problem for you ?". The 4 questions relate to daytime frequency; nocturia; the need to urinate with little warning and question 4 which addresses bladder pain. Each question in the OLS SI is scored 0 for "not at all" to 5 for "usually or almost always" giving a maximum score of 20; each question in the OLS PI is scored 0 for "no problem" to 4 for "big problem"giving a maximum score of 16. The secondary outcome measures were frequency and nocturia as measured by bladder diary and complications such as voiding difficulty. Subjects were randomised to receive, under general anaesthetic, either a 4 minute hydrodistension with injection of 30 mls of normal saline into the bladder wall, or hydrodistension with injection of 500 Units of Abobotulinumtoxin (AboBTXA) diluted in 30 mls of normal saline. Both were injected through a 30 cm Bard 23 gauge needle at 30 sites in 1 ml aliquots, suburothelially sparing the trigone and avoiding ureters. A bladder biopsy was obtained if not already available. Peri-operative antibiotic prophylaxis was utilised.

Urodynamic studies were performed upon recruitment if not available. A free urinary flow rate with post void residual was performed at 1 week post treatment and repeated if elevated. Subjects and treating doctors were blinded to initial treatment allocation. Drug was prepared in the hospital pharmacy according to a series of 3 separate computer generated randomization numbers for each centre, provided by the mathematics department and held confidentially by pharmacy. De-identified syringes were delivered to theatre. One ampoule of Dysport® 500U is variably estimated to be equivalent to approximately 2 to 2 and ½ ampoules of Allergan ®Botox 100U (8,9). Four subjects from 1 centre were randomised and initially received only 200 U of AboBTXA (assumed equivalent to 100U of Botox ®).

Subjects with no improvement after initial treatment had access to AboBTXA treatment if they wished, at a minimum of 3 months after initial treatment as indicated in the flow chart (Figure 1). Patients and doctors remained blinded to their original treatment allocation. Approval for the study was obtained from the Research and Ethics Committees of all 3 hospitals.

Statistical methods

A formal power calculation was not performed prior to the study. The sample size of 50 was chosen to be confident of detecting a 15 % difference in the total O'Leary Sant score between AboBTXA and control groups if present. This was based on the 1 available randomized study at the time which involved 36 refractory subjects. In this study a difference of 16% in global scores was demonstrated when OnaBTXA was compared with BCG injection at 4 weeks and had a 88% excellent response rate (6).

Repeated measures ANOVA was used to test if the BTXA subjects showed improvement in OLS scores and the significance of mean differences at 3 months for each group was determined using paired t test and 95% confidence intervals. SPSS (V19) was used for analysis and statistical significance was set at 0.05 level. Repeated measures ANOVA was used to check for confounding factors.

Measurements continued beyond 3 months, however, further randomized statistical comparisons were not possible as the majority of subjects chose to take up the offer of active AboBTXA injection at or beyond 3 months.

Whether individual subjects had received a benefit was also assessed using a Reliable Change index (RC) to identify those with a statistically significant reduction in scores (10, 11). A clinically significant improvement was defined as a 50% or more reduction in baseline score. This analysis examines whether an individual had a statistically significant change in their score. An interim analysis was performed after enrolment of 20 subjects to exclude adverse effects after one subject reported a marked increase in pain and voiding difficulty.

Results

Fifty four subjects were recruited. One subject was removed prior to randomisation due to a diagnosis of bladder cancer. The mean age was 54 years for the BTXA group and 53 years for the control group; mean parity was 2 for both groups. There was also no difference in BMI with a mean of 27.5 for the BTXA group and 26.6 for the control group. This was a refractory group of IC patients for example, subjects who went on to have AboBTXA treatment had an average of

7 past treatments for IC/BPS (SD 4.6) and the control subjects had an average number of 4 prior treatments. These included but were not limited to; hydrodistension (100% vs 88%), bladder diathermy (25% vs 50%), bladder instillations (92% vs 75%), Tricyclic antidepressants (75% vs 50%), Elmiron (75% vs 50%), and Gabapentin or Pregabalin (58% vs 25%) for the AboBTXA and control groups, respectively.

In addition, the average duration of symptoms for the AboBTXA group was 16 years (SD 9.4) and for control subjects 11 years (SD 4.1). Overall, the mean maximum capacity under anaesthesia was 491 ml (SD 243). The subjects reported multiple other pain syndromes, but treatment allocation and OLS scores were not affected by the presence of these co-morbidities.

The initial diary data analysis excluded 2 AboBTXA subjects without a complete bladder diary. Overall, the average number of voids per day was 13 and by night was 3. The mean maximum functional bladder capacity was 238 mls and mean bladder capacity was 119 mls. Initial urodynamic test results were available for all women. The baseline urodynamic data for the two populations did not differ significantly; the post void residual was not elevated at a mean of 18 ml. First sensation occurred at a mean value of 97 mls and cystometric capacity occurred at a mean value of 178 mls. There were 3 subjects with a detrusor pressure rise over 15 cm water at capacity; no subjects showed a systolic contraction pattern. The mean post void residual urine volume 1 week after initial treatment was 27mls for the control group and 69 mls for the AboBTXA treatment group (NS, p=0.125). Two of the AboBTXA subjects recorded a residual volume over 200mls and in one subject this persisted for 4 weeks.

The OLS problem index (OLS PI) and the OLS symptom index (OLS SI) scores showed significant improvement for both control and BTXA subjects at 6 weeks and 3 months. The OLS PI showed a significantly greater improvement at 3 months in the BTXA group (p=0.04). However there was no improvement in the total OLS score or the OLS SI.

From the mixed model analysis, the estimated means for baseline and 3 months for the control group were 27.8 and 24.9, (change score 2.85, 95% CI [-0.23, 5.91]) and for the AboBTXA group they were 26.5 and 21.2 (change score 5.39, 95% CI [2.30, 8.45]). The difference in total scores for the AboBTXA and control groups between baseline and 3 months was not significant at 2.52, 95% CI [-1.8, 6.9], P=0.25.

A total of 12 subjects had proven UTI detected and treated at some time after cystoscopy and injection; 5 in the control and 7 in the AboBTXA group despite a baseline negative urine culture and peri-operative antibiotic prophylaxis. The presence of UTI was noted to be a confounding factor. If analysis was performed without the UTI subjects as shown in Table 2, there was an overall improvement in the BTXA group in all measurements including the total OLS score (p=0.02), the OLS SI (0.008), the OLS PI (p=0.08) and question 4 of OLS PI addressing the problem of bladder pain (p=0.02).

Only 2 of the control group and 5 of the AboBTXA group had a greater than 50% reduction in the OLS score. Overall, the AboBTXA group had a 20% greater improvement than the control group but this was not significant (P=0.10). Excluding the subjects with UTI led to significantly better response in the AboBTXA group (5/17, 29%) compared to the control group (0/19, 0%, P=.02, Fishers Exact test).

Thirty nine subjects had cold cup bladder biopsy results available. The histology was considered abnormal if there was denudation of surface mucosa or inflammatory infiltrate of macrophages in the urothelium and / or detrusor layer, although detrusor muscle was not always present in the specimen (12). Detrusor mastocytosis was not measured. There was no difference in the primary outcome measures among the 28 out of 39 who showed an abnormal biopsy result compared with those who did not.

Twenty one of the 27 (78%) control subjects requested AboBTXA treatment at or after 3 months compared with 16 of the 26 (62%) of the initial AboBTXA subjects; this was not a significant difference (P=0.16). Subjects and doctors remained blinded to their original allocation. Following this, 9 women (24 %) have requested ongoing treatment. Among these women, study follow up at the time of writing ranged from 0.5 to 72 months (mean 9.1, SD 13.5). These 9 subjects include 7 of the 27 (26%) original control subjects and 2 of the 26 (8%) original AboBTXA group, however this comparison did not reach significance (P=0.08). One subject who remained blinded reported an initial treatment benefit with AboBTXA but failure with a 2nd treatment. None of these 9 subjects have had UTI identified.

There was no significant difference between the three participating hospitals (P=0.45).

The duration of benefit from 1 or multiple AboBTXA treatments, when it occurred has varied from 7 to 57 months.

.

Discussion

In this study, intravesical injection of AboBTXA was not associated with overall improvement in the total OLS score in women with refractory IC/BPS at 3 months albeit an improvement was seen in the OLS problem index (OLS PI). However when a statistical analysis of individuals' change scores was employed, some benefit was observed of the order of 20 % in the OLS score in the AboBTXA compared to the control group which rose to 29% after UTI was excluded.

The randomized study by Kuo et al reported benefit at 3 months using both a pain visual analogue and the OLS questionnaire (13). It is of interest that the same group recently reported no benefit from onaBTXA in a group of patients with ulcer IC which is in agreement with the minimal overall benefit seen in this study (14). El-Bahnasy (6) demonstrated benefit using a pain visual analogue scale. Davies et al found no benefit in a study of 13 subjects with doses of OnaBTXA between 100-300U and 3 of their subjects had urinary retention and exacerbation of their pain (15).

In El-Bahnasy's study there was an unusually high and prolonged overall response rate to treatment with 69% and 88% of those receiving BCG and OnaBTXA respectively still reporting excellent response at nearly 2 years (6). It should be noted that this high response rate to intravesical BCG treatment is far greater than the 11% response for BCG treatment noted by Sairanen (16) so perhaps the study population in El-Bahnassy's trial responded favourably to all treatment modalities.

The subjects recruited for the studies by El-Bahnassy and Kuo were required to have had symptoms for at least 6 months (6,13). This study has recruited a much more refractory group with very long duration of symptoms, multiple failed treatments, mean maximum cystometric

capacity of 178 mls and often an abnormal bladder biopsy which corresponds to the ulcer group in Lee et al who also responded poorly.(14)

UTI was diagnosed using traditional Kass criteria and was common with no difference between the AboBTXA or control groups. The common occurrence of UTI has been noted elsewhere (17), furthermore, antibiotic prophylaxis is not always effective at preventing UTI during follow up. These subjects were not excluded from analysis as the UTI occurred post randomization and treatment. It is difficult to speculate upon the reason for the apparent impact of UTI on response to treatment. The control subjects with UTI had a greater improvement in scores than the BTX group and this confounded the results. Hence, when the analysis was performed excluding the UTI subjects, there was significantly greater improvement in the OLS scores for the BTXA group. It does suggest that there may be a role for infection in the pathogenesis or response to treatment in this group of patients.

This study was pragmatic in design and hydrodistension was offered to both groups. This same approach has been utilized by other centres (13). This was required by all institutional ethics committees involved in the study. Hydrodistension has previously been demonstrated to have an independent beneficial effect over a 3 month period with concomitant reduced secretion of nerve growth factor (18). However, hydrodistension treatment to both groups did not dilute our ability to detect benefit due to AboBTXA treatment alone as no benefit was noted among the hydrodistension and saline injection treatment group.

A weakness of this study is the lack of formal power calculation as at the commencement of the study,limited data was available;it consisted of the El-Bahnasy paper showing an 88% excellent response rate to BTXA. This study is likely to be underpowered for a greater than 50%

improvement. Indeed, the recruitment time of this refractory group of IC/BPS was very long even with this modest sample size of fifty. However, the refractory nature of the condition was thought to be ethically justifiable in order to balance the cost and potential morbidity of BTXA such as urinary retention.

The low incidence of voiding difficulty in this study compares favourably and contrasts with the 42% incidence of voiding difficulty reported after 500 U AboBTXA was used for refractory idiopathic detrusor overactivity (19). In our study, residual urine volumes were significantly raised in the AboBTXA group compared with the control group; however only one of the subjects had worsening pain and prolonged voiding difficulty over a 4 week period. This was despite the frequent finding of reduced flow rates on the pre treatment assessment.

Dosage is unlikely to have been an issue, as previous studies have demonstrated benefit using widely differing dosages.

Nine (24%) of the subjects have requested a 2^{nd} (7 of the original control group) or 3^{rd} (2 of the original BTXA group) ongoing treatment over 2 years following their initial randomization treatment. While the drug was provided free of charge, this does suggest some benefit for this subset of patients. AboBTXA may be an effective treatment for a small minority of refractory subjects. While women with refractory IC/BPS remain one of the most difficult patient groups to treat, it could be argued that any safe therapy with even limited effectiveness is worth consideration.

Conclusion

For chronic refractory IC/BPS patients, there was no overall improvement in the mean OLS score after injection of abobotulinum toxin and hydrodistension versus saline injection with hydrodistension. The subgroup with no urinary tract infection had significant benefit in all OLS scores. This study found that intravesical injection of AboBTXA was an effective treatment in halving the OLS score for a only a small minority of women with refractory IC/BPS.

References

[1] Smith C, Radziszewski P, Borkowski A, Somogyi G, Boone T, Chancellor MB. (2004). Botulinum toxin a has antinociocpetive effects in treating interstitial cystitis. Urology , 64[5], 871-875.

[2] Giannantoni A, Porena M, Costantini E, Zucchi A, Mearini L, Mearini E. (2008). BotulinumA toxin intravesical injection in patients with painful bladder syndrome: 1-year followup. Journal Urology. 179[3], 1031-1034.

[3] Ramsay AK, Small DR, Conn IG. (2007). IntravesicalBotulinum toxin type A in chronic interstitial cystitis: results of a pilot study. Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland, 5[6], 331-333.

[4] Chuang YC, Yoshimura N, Huang CC, Chiang PH, Chancellor MB. (2004). Intravesical Botulinum Toxin A administration produces analgesia against acetic acid induced bladder pain responses in rats. Journal Urology. 172[4], 1529-1532.

[5] Pinto R, Silva A, Lopes T, Silva JF, Silva CM, Cruz FR, Dinis PO. (2009). Intra-trigonal injection of Botulinum toxin A in patients with bladder pain syndrome.Results at 9 months of follow-up. Journal Urology, 181[4,supplement], 20.

[6] El-Bahnasy AE, Faharat YA, El-Bendary M, Taha MR, El-Damhogy M, Mourad S. (2005). A randomised controlled trial of Bacillus Calmette-Guerin and Botulinum Toxin A for the treatment of refractory interstitial cystitis. UIJ, 12[6], 1944

[7]. Gillenwater JY, Wein AJ. (1987). Summary of the National Institiute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial cystitis, National Institiutes of Health, Bethesda, Maryland, August 28-29, Journal Urology, 1987, 140, 203-206.

[8]. Karsai S., Raulin C. (2010) Botox and Dysport: Is there a dose conversion ratio in dermatology and aesthetic medicine? J American Academy of Dermatology, 62[2].346-347.

[9] Manstein C, Beidas OE. (2011) Comparing Clinical Efficacy of Botox and Dysport in a Small Group of Patients. Plastic and reconstructive surgery , 128[1], 26e

[10] Jacobson, NS, Truax, P. (1991) Clincial Significance: A Statistical Approach to Defining Meaningful Change in Psychotherapy Research, J. Consulting and Clinical Psychology, 59(1), 12-19.

[11] Deyo, RA, Diehr, P, Patrick, DL. (1991) Reproducibility and Responsiveness of Health Status Measures, Controlled Clinical Trials, 12, 142S-158S

[12] Van de Merwe J NJ, Bouchelouche P, Bouchelouche K, Cervigni M, Daha L, Elneil S, Fall M, Hohlbrugger G, Irwin P, Mortensen S, van Ophoven A, Osborne J, Peeker R, Richter B, Riedl C, Sairanen J, Tinzl M, Wyndaele J-J. (2008). Diagnostic Criteria, Classification, and Nomenclature for Painful Bladder Syndrome/Interstitial Cystitis: An ESSIC Proposal. European Urology, 53, 60-67.

[13] Kuo HC. (2010 questionnaire) Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis.Urol Int. 75, 170-174.

[14] Lee CL, Kuo HC (2013) Intravesical botulinum toxin a injections do not benefit patients with ulcer type interstitial cystitis. Pain Physician. 16(2):109-16.

[15] Davies A, Chahal R, Inman R, Urwin G. (2006). Intravesicalbotulinum A toxin (Botox)-- does it have a role in the management of interstitial cystitis. European Urology, Supplement 5[suppl 2], 22.

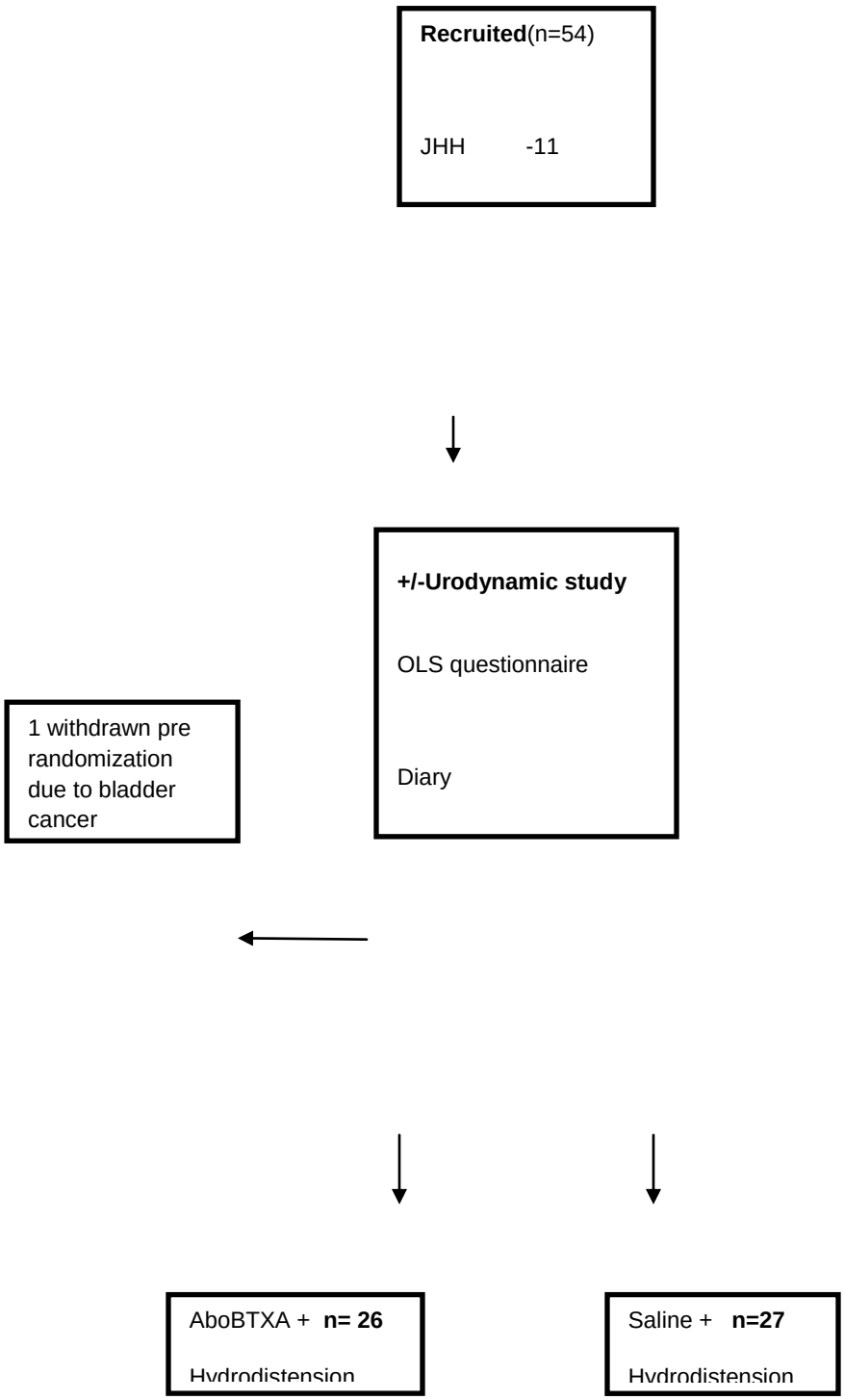
[16] Sairanen J., Leppilahti M. ,Tammela TL., Paananen I., Aaltomaa S., Taari K., Ruutu M. (2009) Evaluation of health-related quality of life in patients with painful bladder syndrome/interstitial cystitis and the impact of four treatments on it. Scand J Urol. Nephrol. 43[3], 212-219.

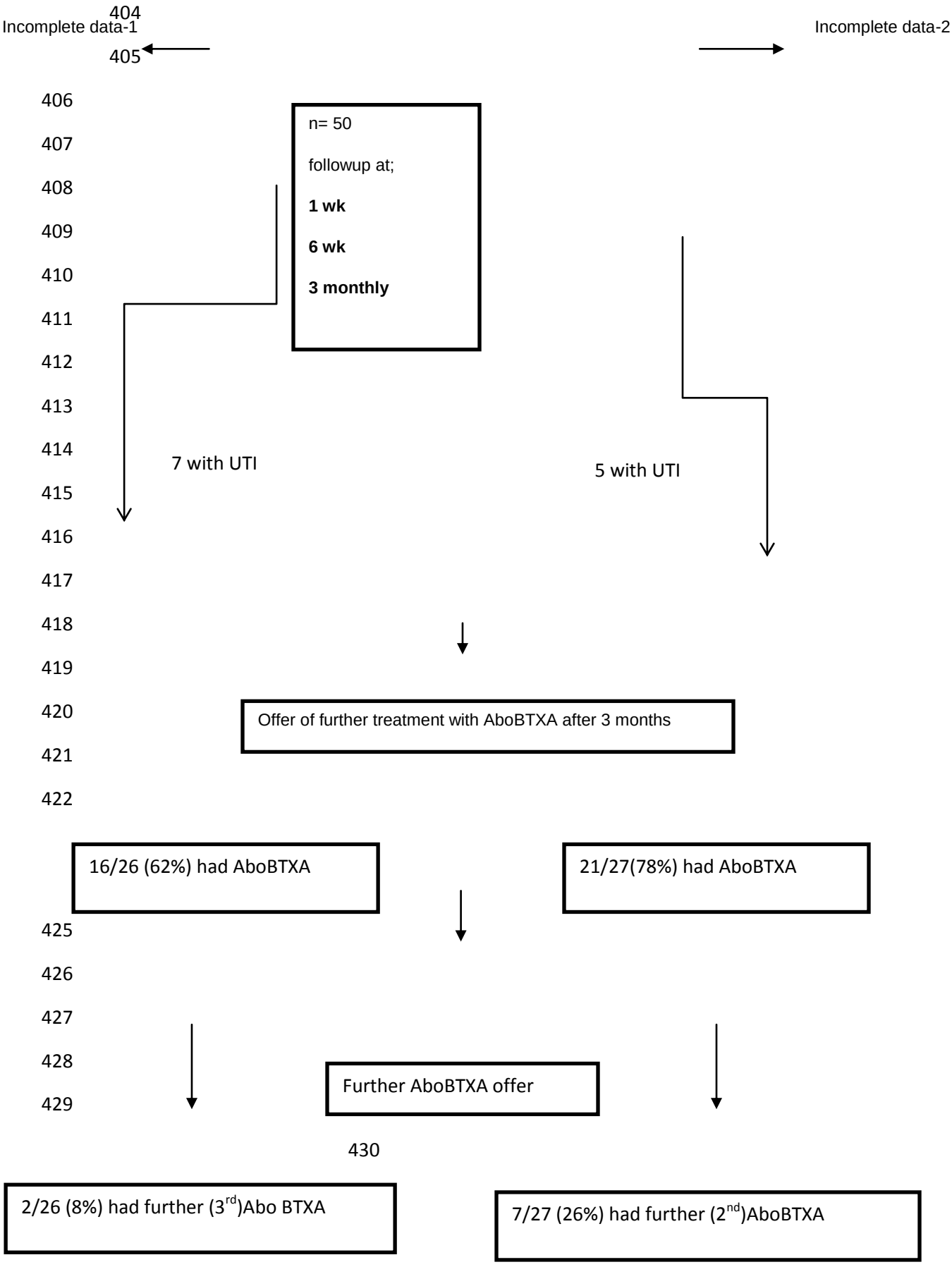
[17] Flynn MK., Amundsen CL., Perevich MA., Liu F., Webster GD., (2009) Outcome of a randomized, double blind, placebo controlled trial of Botulinum A toxin for refractory overactive bladder J Urol, 181 (6):2608-15

[18] Liu HT, Tyagi P, Chancellor MB, Kuo HC. (2009) Urinary nerve growth factor level is increased in patients with interstitial cystitis/ bladder pain syndrome and decreased in responders to treatment. BJU international, 104[10], 1476-1481.

[19] Jeffrey S, Fynes M, Lee F, Williams L, Morley R. (2007) Efficacy and complications of intradetrusor injection with botulinum toxin A in patients with refractory idiopathic detrusor overactivity. BJU international. 100[6], 1302-1306.

Figure 1; Flow chart




404
Incomplete data-1
405
Incomplete data-2
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
n= 50
followup at;
1 wk
6 wk
3 monthly
7 with UTI
5 with UTI
Offer of further treatment with AboBTXA after 3 months
16/26 (62%) had AboBTXA
21/27(78%) had AboBTXA
425
426
427
428
429
Further AboBTXA offer
430
2/26 (8%) had further (3rd)Abo BTXA
7/27 (26%) had further (2nd)AboBTXA

431

Table 1; Treatment outcome for subjects receiving BTXA+ hydrodistension versus saline + hydrodistension at baseline and 3 months.

	Treatment allocation	Baseline mean (SD) or [95% CI if available]	3 months post treatment mean (SD) or [if available 95%CI]	Mean difference and 95% CI	p
Voids/day	AboBTXA	13.5 (7.1)	10.4 (5.8)	3.2 [1.1-5.3]	0.25
	Control	12.5 (5.4)	11.4 (4.4)	1.5 [-0.7- 3.6]	
Voids/night	AboBTXA	3.2 (1.6)	3.3 (2.2)	0.13 [-0.8-1.1]	0.85
	Control	3.2 (2.6)	2.3 (1.7)	0.25 [10.6-1.1]	
Average capacity (mls)	AboBTXA	120 (84)	157 (94)	-29.1 [-73.0-14.8]	0.31
	Control	118 (52)	119 (68)	-5.1 [-28.1-17.8]	
Maximum Capacity (mls)	AboBTXA	242 (166)	273 (152)	19.6 [-2.7-41.8]	0.27
	Control	233 (96)	210 (84)	-18.0 [-85.4-49.5]	
OLS problem Index	AboBTXA	13.6 [CI 12.5-14.6]	9.9 [8.3-11.6]	3.64 [1.58-5.70]	0.04
	Control	13.7 [CI 12.7-14.9]	12.8 [11.0-14.3]	1.00 [-0.44- 2.44]	
OLS symptom Index	AboBTXA	13.2 [CI 12.1-14.2]	10.5 [8.7-12.3]	2.7 [0.7-4.6]	0.30
	Control	13.9 [CI 12.9-15.1]	12.3 [10.6-14.3]	3.6 [1.6-5.7]	
OLS Q 4 pain	AboBTXA	3.6 [CI 3.3-4.0]	2.8 [2.3-3.7]	0.8 [0.2-1.2]	0.09
	Control	3.6 [CI 3.2-4.0]	3.4 [2.9-4.0]	0.17 [-2.4-0.6]	
Total OLS score	AboBTXA	26.7 [CI 24.7-28.7]	20.4 [17.1-23.7]	3.7 [-0.34-7.6]	0.12
	Control	27.8 [CI 25.8-30.0]	25.3 [21.9-28.8]	-1.5 [-0.2-2.2]	

TABLE 2 ;

Treatment outcome for subjects without UTI receiving BTXA+ hydrodistension vs saline + hydrodistension at baseline and at 3 months

Without UTI (n=38)	Treatment	Baseline score [95% CI]	3 months score [95% CI]	Mean Difference (pre-post) and [95% CI]	P
OLS score	Abo BTXA	26.9 [24.5-29.3]	20.8 [17.1-24.6]	6.1 [2.5-9.6]	0.02
	Control	27.4 [25.1-29.7]	27.3 [23.6-30.9]	0.16 [-3.3-3.6]	
OLS SI	Abo BTXA	13.1 [11.8-14.3]	10.7 [8.7-12.7]	2.4 [0.6-4.2]	0.008
	Control	13.6 [12.4-14.9]	13.6 [11.6-15.5]	0.05 [-1.7-1.8]	
OLS PI	Abo BTXA	13.8 [12.5-15.1]	10.2 [8.3-12.0]	3.7 [1.7-5.6]	0.08
	Control	13.8 [12.5-15.0]	13.7 [11.9-15.5]	0.1 [-1.8-2.0]	
OLS PI Q4 "problem of pain"	Abo BTXA	3.8 [3.4-4.2]	2.9 [2.3-3.5]	0.89 [0.29-1.4]	0.02
	Control	3.5 [3.1-3.9]	3.7 [3.1-4.3]	-0.16 [-0.74-0.42]	