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Effect of Alprazolam in Spasticity: A Pilot Study

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Abstract

Background: Alprazolam, given in 0.5 mg dose for some other reason (like anxiety), showed reduction in spasticity and spasm lasting for a few hours. On searching the literature we did not come across any study to authenticate this effect of alprazolam. Hence, this study was planned.

Methodology: This was a prospective pilot study. 38 cases suffering from spasticity of any origin were included. 0.5 mg (for 15 days) followed by 1mg (for another 15 days) of Alprazolam once daily ½ hour before bed time was given to every patient and repeat evaluations were done at day 15 (0.5mg) and 1 month (1mg). Spasticity were assessed by MAS, PSFS, Peak torque at 30º, 60º, and 90º/sec, time taken for ADL drinking, dressing, hand activity), and FIM motor score.

Results: 34 completed the 1 month period of study. Significant improvement was observed in MAS score, PSFS at each time, peak torque at 30º /sec velocity (only with 1mg), peak torque at 60º and 90º /sec, FIM score, drinking activity (only with 1mg), dressing activity and hand activity.

Conclusion: Alprazolam is a safe and effective drug for the treatment of spasticity as well as spasms, that is, both the phasic and tonic part of stretch reflexes responds to alprazolam when used up to 1 mg for 1 month. Performance of ADL improved favorably with 0.5 and 1 mg alprazolam. Further studies are required in this area regarding the long term safety and efficacy and effective dose for spasticity.

Key words: Spasticity, Alprazolam, FIM, MAS, PSFS

Introduction

Spasticity is a motor disorder characterized by a velocity dependent increase in tonic stretch reflexes with exaggerated tendon jerks, resulting from hyper-excitability of the stretch reflex, as one component of the upper motor neuron syndrome[1]. Spasticity is associated with some very common neurological disorders like multiple sclerosis, stroke, cerebral palsy, spinal cord injury, brain injuries, and neurodegenerative diseases. Although the exact incidence of spasticity is unknown, it is likely that it affects more than half a million people in the United States alone, and more than 12 million people worldwide[2]. Following stroke, approximately 65% of individuals develop spasticity[3]. Roughly, 70% of persons with spinal cord lesion are spastic one year after injury and around half of these receive antispastic medication[4].

Spasticity can cause discomfort, stiffness, pain, pressure sore and difficulty in performing physical activities such as walking, transferring, picking up objects, washing, dressing and sexual activity can all be affected with increase muscle tone. Poorly managed spasticity can also be responsible for muscle shortening and the development of tendon and soft tissue contractures, which together with spasms can lead to compromised safety in lying and sitting[5]. Contractures are responsible for major functional implications, including difficulties with personal hygiene or dressing, positioning, and at times the inability to sit, which may lead to restricted community mobility and social isolation.

While managing some patients having spasticity, alprazolam was given to these patients in the dose of 0.5mg at bed time for some other reason, like insomnia or anxiety. It was noticed that these patients showed reduction in spasticity and spasm lasting for a few hours. On searching the literature we did not come across any study to authenticate this effect of alprazolam. Hence

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working on this finding that alprazolam may have a role in the reduction of spasticity, we planned this study.

Methodology

It was a prospective pilot study. Aims and objectives of the study were to find out whether alprazolam given in the dose of 0.5 mg or 1 mg once daily at bed time, has any effect on muscle tone in patients suffering from spasticity of any origin. 38 Consecutive cases, satisfying our inclusion criteria, attending PMR out-patients at AIIMS, New Delhi, (between December 2006 and July 2008), suffering from spasticity of any cause, in whom spasticity was interfering in activities of daily living or causing any discomfort where treatment of spasticity was warranted were included in this study. The patients were not treated simultaneously with any other drug for spasticity at the time of recruitment into the study, except for baclofen. If baclofen alone was being given earlier, alprazolam was started only in case the effect of baclofen in reducing spasticity was inadequate and if there was a need to enhance the dose of the baclofen or add another drug for treating spasticity. In such a case the dose of baclofen was maintained as per the previous level and alprazolam was added.

Inclusion criteria: Age above 12 years of both sexes, all old and new diagnosed cases of spasticity from any underlying cause requiring treatment of spasticity and patient not taking any other drugs that affect muscle tone except baclofen.

Exclusion criteria: Unwillingness to participate, any kind of deformity and/ or contracture, any other acute medical condition and significant cognitive dysfunction which might interfere in assessment of spasticity or ADL assessment. Major psychiatric disorder and patient on anti psychotic medicine and any acuteness of the condition that may interfere with the patient's level of spasticity, like acute urinary tract infection, in-growing toe nail, pressure ulcer etc. Patient suffering from Myasthenia gravis or acute narrow angle glaucoma and pregnant females and infants were also excluded.

All patients were explained about the procedure to dispel and correct misconception. They were explained about harms and benefits of the alprazolam. Informed written consent was taken from all patients and from parents in case of minors in this drug trial. Following investigations were done for every patient at base line and follow-up: Complete haemogram (Hb, DLC, TLC and ESR), Liver function test (SGOT, SGPT, and ALP), Kidney function test (serum urea and creatinine) and urine routine and microscopy. Other investigations were done depending upon the clinical condition.

Intervention: A dose 0.5 mg of alprazolam once daily ½ hour before bed time was given to every patient, included in the study. The repeat evaluation was done at day 15. At the end of 15 days, if no significant improvement was seen in ADL till the level where further treatment was not warranted, so the dose was increase to 1 mg and repeat evaluation was done after another 15 days. If no response was seen and or any untoward effect was noted at the end of one month study, the drug was stopped. All the patients were subjected to regular passive range of motion (150 repetitions) of all joints of upper and lower limb affected with spasticity and one week was taken to optimize the effect of physiotherapy on the patient before starting drug evaluation.

Spasticity assessment: In each assessment session, the spasticity was assessed by the following tools:

(1) Clinical assessment: was done by using Modified Ashworth Scale and Penn Spasm Frequency Scale.

Spasticity was scored with MAS by setting grade 1 to 1, grade 1+ to 2, grade 2 to 3, grade 3 to 4 and grade 4 to 5 as Skold et al[6] had done, for all the affected muscle groups in extremities (hip, knee, ankle, shoulder, elbow, and wrist). All patients were evaluated for MAS[7] under same circumstances, (time of the day, ambient temperature, testing position-lying down position). If any patient was affected with some general health (such as urinary tract infection, constipation, pain, fatigue) during follow-up then such patient was excluded from study.

The PSFS[8] is based on self-reporting by using a scale from 0 to 4, with the following rankings: 0, no spasm; 1, mild spasms induced by stimulation; 2, infrequent full spasms occurring less than once per hour; 3, spasms occurring more than once per hour; and 4, spasms occurring more than 10 times per hour. A complete history about spasm frequency was taken, patients were advised to note the frequency of spasm / fall, whether it was decreasing or not during treatment period.

(2) Biomechanical method (by Isokinetic dynamometer): Peak torque responses were assessed at 30º, 60º and 90º/sec of angular velocity at knee joint (flexion and extension) on continuous passive motion mode (with computerized isokinetic dynamometer-Biodex system-2)[9,10,11,12], at each assessment session. Assessment was done in the sitting position with 15º seatback tilt and in the morning hours (10:00 am) before patients had undergone any therapeutic activity. Alignment of knee axis of rotation with power-head shaft was done with a line drawn in the sagittal plane through the femoral condyles to mechanical axis of dynamometer. Calf pads were placed 4 cm proximal to the lateral malleolus. Patient was stabilized with thigh strap, pelvic strap and shoulder

straps across the chest. The test program was selected and data were entered. Each trial was conducted through 90º range of motion of knee joint at each angular velocity and same ROM was used at each follow-up. Ten consecutive passive joint motions were performed at three pre-selected angular velocities (30, 60, and 90º/sec) for affected knee joint. Gravity correction option was in built in the Biodex machine, was undertaken. Resistance to passive motion was determined for both knee flexor and extensor muscle groups by the maximum peak torque values among ten repetitions. Average of maximum peak torque for each patient was calculated by summing the two or four maximum peak torques and then divided by 2 or 4 according to affected extremities, for all three velocities at base line, 1st follow-up and 2nd follow-up.

(3) ADL Assessment: Patients were assessed for three ADL and time taken in these activities was noted with stop watch in seconds. Time taken in picking a glass of water from table to putting it on lips with each hand separately, time taken in lower extremity dressing with or without assistive devices and time taken in picking a book from one corner of table to putting it on another corner with each hand separately were measured initially and at follow-up. Same glass, clothes and book were used.

(4) Functional Independence Measure (FIM): FIM motor score was used to assess improvement in one's ability to function with independence at base line and at follow-up as used by sipski ML et al[13] and P. Azouvi et al[14]. The best and worst possible FIM motor sub-score is 91 and 13 respectively. Total FIM motor score was compared at base line, at 15 day and 1 month.

Statistical Analysis Descriptive statistics like mean, median, minimum, maximum and standard error were calculated for each of the quantitative variables. Repeated measure ANOVA/Friedman test for testing the significance of change in various variables was used. In case of significant result, multiple comparison tests was done by Post hoc by using Bonferroni /adjusted Wilcoxon signed ranks test. For categorical data like Penn Spasm Frequency scale, Mc-Nemar test was used. A result was considered significant at 5% level of significance, that is, $p<0.05$.

Results

38 subjects were enrolled, only 37 and 34 completed 15 day and 1 month follow-up period respectively. The patients were contacted through telephone for follow-up. The reasons for drop-out were side effect of alprazolam (1), difficulty in transport (1) and loss of health due to other causes (1). One case was lost to follow-up and could not be contacted.

Demographic distribution:

Age and Sex: The age distribution of the 38 subjects (29 males, 9 females) included in this study varied from 16 -65 years, with the mean of 33.92 ± 15 years.

Case profile:-Based on the site of lesion patients were divided into three neurological groups namely cerebral, cervical and dorso-lumbar. 22 had lesion in dorso-lumbar region, 8 had lesion in cervical region and 8 were those where spasticity was of cerebral origin. In spinal origin of spasticity, most cases were spastic due to traumatic spinal cord injury (table 1).

	Cause of spasticity	*No. of patients*
1.	Cerebral palsy	3 (7.89%)
2.	Traumatic brain injury	3 (7.89%)
3.	Space occupying lesion in brain	1 (2.63%)
4.	Traumatic Spinal cord injury	16 (42.11%)
5.	Compressive myelopathy	9 (23.68%)
6.	Pott's paraplegia	4 (10.53%)
7.	Non-compressive myelopathy	1 (2.63%)

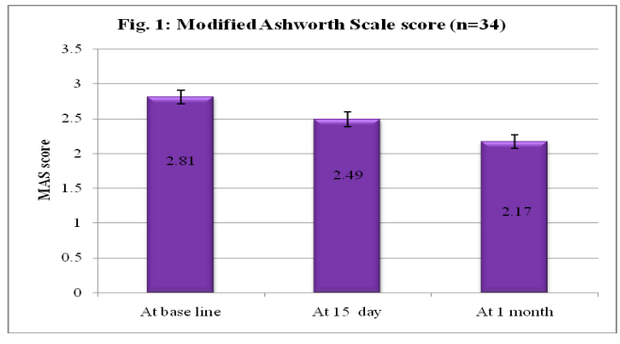
Table 1: Causes of spasticity (n=38)

Duration of spasticity:- Mean duration of spasticity was 48.80 ± 76.55 months, with a range 15 days to 288 months. Most (n=16) of patients had spasticity for duration of less than 6 months.

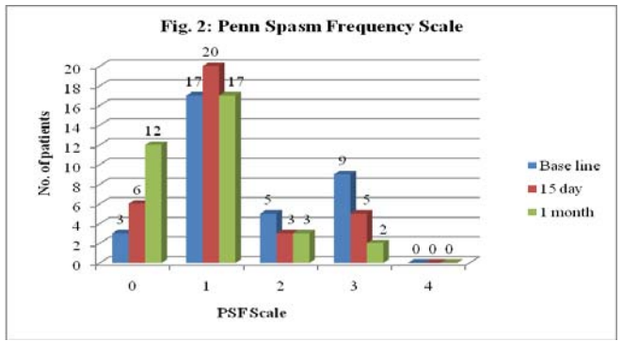
Treatment received: Out of 34 cases that completed the study, in 29 cases alprazolam was given alone. Rest 5 cases, were those where baclofen being given earlier, in such case the dose of baclofen was maintained as per the previous level and alprazolam was added.

Modified Ashworth Scale (MAS): Mean MAS scores at base line, 1st and 2nd follow up were 2.81 ± 0.098, 2.49 ± 0.11, and 2.17 ± 0.099 respectively. There was significant improvement in MAS (p =0.0001). Significant improvement in spasticity as measured by MAS was also seen, when comparison was done between base line and 1st follow-up, base line and 2nd follow-up and 1st follow-up and 2nd follow-up (fig 1).

Penn Spasm Frequency Scale (PSFS) score: Significant improvement in PSFS score was seen, when



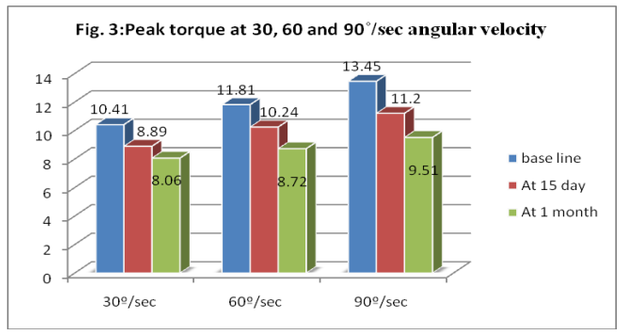
comparison was done between base line and 1st follow-up (p=.0234), 1st follow-up and 2nd follow-up (p=.0148) and between base line and 2nd follow-up (p=.0019). At base line out of 34 cases, 20 cases belonged to 0 and 1 PSFS, which increased to 26 at 1st follow-up and further increased to 29 at 2nd follow-up (fig 2).

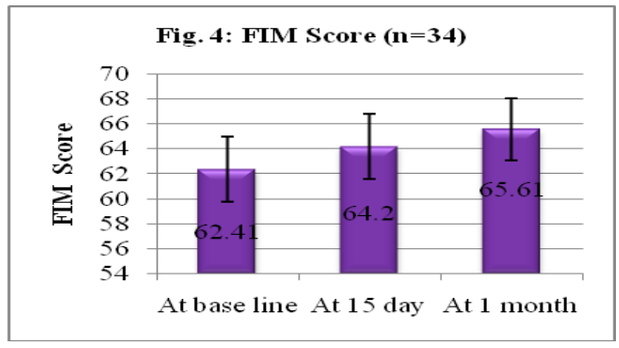


Biomechanical assessment of spasticity using Isokinetic dynamometer: Peak torque at 30°/sec angular velocity: Mean peak torque during base line, 1st and 2nd follow up are shown in table 2 and figure 3 at 30°/sec, 60°/sec, 90°/sec angular velocity. Significant (p=0.018) decreased in mean peak torque at 30° /sec angular velocity was seen only when comparison was done between base line and 2nd follow-up. **Peak torque at 60°/sec angular velocity:** There was significant (p=.001) decrease in mean peak torque at 60°/sec angular velocity. Significant decrease in mean peak torque at 60°/sec angular velocity was also seen, when comparison was done between, base line and 2nd follow-up (p=.006) and 1st and 2nd follow-up (P = .014). When comparison was done between base line and 1st follow-up, it was borderline non-significant (p=.053) improvement. **Peak torque at 90°/sec angular velocity:** significant decrease in mean peak torque at 90°/sec angular velocity (p=.0001). Significant decrease in mean peak torque at 90°/sec angular velocity was seen, when comparison was done between base line and 1st follow-up (p=.009), base line and 2nd follow-up (p=.001) and 1st and 2nd follow-up (P = .011)

	Atbase line	At15 days	At1 month	1-2	2-3	1-3	P value
Mean ± S E at 30°/sec	10.41±1.22	8.89±.663	8.06±.672	NS	NS	*	0.018
Mean ± S E at 60°/sec	11.81±1.42	10.24±1.06	8.72±.82	NS	*	*	0.001
Mean ± S E at 90°/sec	13.45±1.50	11.2±1.13	9.51±.89	*	*	*	0.0001

Table 2: Peak torque (n=34). (N-number of cases, S.E-Standard error, 1=Base line, 2=1st follow-up, 3=2nd follow-up, NS = Non significant, *=Significant at 5% interval between baseline and the corresponding follow-ups)





Functional Independence Measure: Mean FIM motor scores at base line, 1st and 2nd follow up assessment were 62.41 ± 2.623, 64.2 ± 2.581 and 65.61 ± 2.484 respectively (Fig. 4) Significant increase in mean FIM motor score was seen (p=.0001). Improvement was seen mainly in lower extremity dressing, transfer, and bathing. Significant increase in mean FIM score was obsorved when comparison was done between base line and 1st follow-up (p=.0001), base line and 2nd follow-up (p=.0001) and 1st and 2nd follow-up (p = .0001).

Time taken in Lower Extremity dressing: The descriptive statistics of base line and follow-up cases are shown in table 3. Significant decrease in mean time taken in lower extremity dressing (p=.001) was seen. Significant decrease in mean time taken in lower extremity dressing was seen when comparison was done by using post hoc/ adjusted wilcoxon signed ranks between base line and 1st follow-up, base line and 2nd follow-up and 1st and 2nd follow-up.

Time taken in hand activity: Time taken in drinking activity: All cases where lesion was in dorso-lumbar region of spinal cord were excluded for analysis. At base line, only 8 patients were able to perform this activity excluding. At 1st follow-up, one case dropped and one patient who was not able to perform initially, started performing this activity. Analysis was done, it showed significent improvement in median time taken in this activity only when comparision was was done between base line and 2nd follow-up (p=.026) (Table 4).

Time taken in picking a book At base line, only 8 patients were able to perform this activity (pareplegic were excluded). Analysis was done for 7 patients,

	Atbase line	At15 days	At1 month	P value=.0001		
				1-2	2-3	1-3
Mean± SE	159.78±42.15	108.6±23.45	75±14.23	*	*	*
Median	85.00	60.00	40.00			
Min-Max	15-720	13-420	10-240			

Table 3: Time (sec.) taken in Lower Extremity dressing (n=23). (n-number of cases, S.E-Standard error, 1=Base line, 2=1st follow-up, 3=2nd follow-up, *=Significant at 5% interval between baseline and the corresponding follow-ups)

	Atbase line	At15 days	At1 month	P value=0.026		
				1-2	2-3	1-3
Mean± SE	14.14±3.82	11.57±2.61	9.57±2.71	NS	NS	*
Median	12.00	12.00	8.00			
Min-Max	5-35	4-25	3-25			

Table 4: Time (sec.) taken in drinking activity ((n=31). (n-number of cases, S.E-Standard error, 1=Base line, 2=1st follow-up, 3=2nd follow-up, NS = Non significant, *=Significant at 5% interval)

	Atbase line	At15 days	At1 month	P value=0.003		
				1-2	2-3	1-3
Mean± SE	21.14±7.64	17.14±6.82	8.0±1.52	*	*	*
Median	17.00	12.00	8.00			
Min-Max	5-62	4-56	3-16			

Table 5: Time (sec.) taken in hand activity: (n=31). (N-number of cases, S.E-Standard error, 1=Base line, 2=1st follow-up, 3=2nd follow-up, *=Significant at 5% interval between baseline and the corresponding follow-ups)

excluding 1 drop-out case and there was significant decrease in median time taken to perform this activity (p=.003). Significant decrease in median time was seen, when comparison was done between base line and 1st follow-up, base line and 2nd follow-up and 1st and 2nd follow-up (Table 5).

Reported Adverse Events: Out of 38 patients, 19 reported adverse event during treatment, i.e. mild drowsiness in 9 patients, light headache in 4 patients, both light headache and drowsiness in 3 patients, and dry mouth in 3 patients. All these side effects were mild and did not warrant drug discontinuation, except in one case where drowsiness was more marked and patient could not tolerate the increased dose of alprazolam. This patient was excluded from study and drug was withdrawal gradually. All side effects were generally observed at the beginning of drug treatment, mostly at night and morning hours and disappeared in most of cases with continuation of medication (with range of 3-12 days). In 3 cases these side effect were observed with increment of dose from .5 to 1 mg (for a range of 5-7 days).

Discussion

To our knowledge this is probably the first study to evaluate the effect of alprazolam on spasticity. Alprazolam, a triazolobenzodiazepine derivative is mainly used as an anxiolytic, in panic attacks and in panic disorder with or without agoraphobia. On searching the literature we did not come across any study to authenticate this effect (antispastic) of alprazolam. Hence working on this finding that alprazolam may have a role in the reduction of spasticity, we planned this study.

The results of our study showed that there was significant reduction in spasticity and spasm with 0.5 and 1 mg alprazolam, given half an hour before bed time as measured by many of the standardized measures of spasticity i.e. MAS, PSFS, passive peak torque at 30º, 60º and 90º/sec angular velocity, FIM motor score, and in ADL activities.

In our study spasticity, as measured on MAS, decreased significantly after treatment with alprazolam ($p < .0001$) in dose dependent manner. Mean MAS decreased from 2.81 ± .098 (S.E) to 2.49 ± .11 with 0.5 mg of alprazolam given for 15 days, and further reduced down to 2.17± .099 With 1 mg. for another 15 days. Similar improvement in MAS was also reported in previous studies with various anti-spasticity medications. Nance PW[15], reported that MAS was significantly reduced ($p = 0.0001$) by tizanidine treatment in spinal cord injury patients. Guillaume D[16] noted that patients with spinal origin spasticity, MAS decreased in lower extremities from 3.68 ± 0.81 to 1.92 ± 0.75 ($p < 0.001$) and in upper extremities from 1.65 ± 0.78 to 1.34 ± 0.50 ($p < 0.001$), after intrathecal baclofen treatment with 3, 6, 9 and 12 month follow-up. Mueller et al[17] noted that MAS reduced significantly after treatment with Gabapentin 400 mg, given three time in a day in 15 patient with multiple sclerosis ($p = 0.007$). Since similar improvement in Modified Ashworth Scale was noticed in our study, Alprazolam may have role in treatment of spasticity like other oral medication (i.e: Tizanidine, intrathecal Baclofen, and Gabapentin).

We observed significant decrease in frequency of spasm score with 0.5 mg of alprazolam for 15 days (p=.0234) and further decrement was reported after increment in dose by 0.5 mg for another 15 days (p=.0019). In our study, most of the improvements in spasm were reported during night time. This could be due to short duration of

action of drug or because of alleviation of anxiety, which may aggravate spasms. Decrement in PSFS after alprazolam, again go in the favor of antispastic effect of alprazolam. PSFS decreased significantly with antispastic medications in various studies, like our study. Neill[18], reported that 3 of 4 patients had greater improvement of spasms on diazepam given at dose 16 mg/day, increasing after 1 week to 24 mg/day, continued for a further 1 week, in multiple sclerosis patients. Kathleen Hawker[19] reported that PSFS score was reduced from 2.7 ± 0.65 to 0.9 ± 0.29 with levetriacetam treatment in multiple sclerosis.

In our study we found peak torque decreased significantly at 30º, 60º and 90º per sec. of angular velocity with 1 mg of alprazolam. But we did not find any significant improvement at 30º/sec. angular velocity when alprazolam was given in a dose of 0.5 mg. Similar results were also reported by Perell K[20], he found significant decrease in peak torque at 60º and 90º per sec. of angular velocity in spinal cord injury (spastic patients) as compared to control group, but not at 30º per sec angular velocity. This can be explained by the definition of spasticity itself, that spasticity is a velocity-dependent increase in tonic stretch reflexes that is, at lower angular velocity less stretch reflex will be generated and so why less peak will be obtained, so decrement in peak torque at 30º/sec may not be significant with treatment. In our study we also found that peak torque had a linear relationship with angular velocity. We also found there was significant correlation between peak torque and MAS, like MN Akman[21] who also reported similar finding.

In this study we assessed only motor part of FIM score because we expected that after drug treatment, motor power of affected extremity would increase, which was previously hindered by increased muscle tone. Study result showed significant improvement in functional status of spastic patients with Alprazolam as measured with FIM motor score and time taken to perform some common ADL. We observed most of the improvements in lower extremity dressing, turning in bed, , bathing and transfer, mainly observed in patients where motor power was not completely lost and or spasticity hindered the motor power like; incomplete SCI, compressive or non compressive myelopathy etc, in a dose dependent manner. Though the separate analysis was not done but improvement in FIM motor score was mainly observed in patients who had lesion in dorso-lumbar region of spinal cord. Similar finding was also observed by Dario A[22]. He observed significant improvements in FIM scores in 20 patients with severe spinal spasticity after treatment with chronic intrathecal baclofen infusion. Improvements were mainly in bathing, dressing lower body, and transfer. In our study the mean FIM motor score improvement was less (3-3.5 score), this could be because of short duration of treatment or may be because of inadequate dose of drug. Similar result was also reported by P. Azouvi[42] in sever spastic SCI patients with intrathecal baclofen. We found similar improvement in FIM score, so results of our study showed that alprazolam might have similar effect in improvement of once ability to function with independence compared to intrathecal baclofen.

The current established safety and pharmacokinetics profile of alprazolam suggest that it might be well tolerated in patients with spasticity, who typically required treatment with multitude of drugs, there by placing them at risk for drug interaction and adverse events, including cognitive dysfunction. In this study we observed that alprazolam had effect on spasticity and spasm as well with fewer reported adverse events which were mild and well tolerated and did not require drug discontinuation, with the exception of one patient where drowsiness was marked and patient was excluded from study, as compare Cocchiarella et al[23], observed while studying 19 spastic subjects, that many of the participants experienced fatigue and drowsiness, which resulted in 5 subjects dropping out of the study while taking diazepam and in another study of 12 spastic subjects, it was observed that ambulation speed was negatively affected[24] with diazepam treatment due to drowsiness and fatigue caused one subject to withdraw from the study. Alprazolam also showed improvement in one's ability to function with independence and many of the activity of daily living with minimum side effects at this dose. So this might be a useful drug in treatment of spasticity compared to other drug used for the treatment for spasticity. Alprazolam is also a cost effective drug compared to other drugs, used for treatment of spasticity. Rather than reducing spasticity it is also helpful in reducing anxiety and insomnia that are commonly associated with stroke and spinal cord injury patients.

Conclusion

It can be inferred from our study that: Alprazolam was safe and effective drug for the treatment of spasm and spasticity of any origin and had milder and tolerable side effects when used up-to 1 mg of dose, for the treatment of spasticity. Performance of activities of daily living like dressing, transfer, hand activity, hygiene, bathing, turning in bed and one's ability to function with independence, improved favorably with .5 and 1 mg alprazolam. It is easily available and cheaper drug compared to other anti-spasticity drugs.

Recommendations

In this study Alprazolam was given only for a period of 1 month, further studies are required to establish the long

term efficacy and safety profile and tolerance of alprazolam. In this study the number of patients was small, so before generalization of the results, further studies are required involving large number of patients. Further studies are required in the area regarding the effect of alprazolam on spasticity of specific underlying cause, because in this study we included all the cases of spasticity that satisfied our inclusion criteria's. Cost effective analysis of alprazolam was not done with other available antispastic medications, it could become the scope of future studies. Significant improvement in spasticity and spasms were observed mainly during night time and morning hours. As we measured spasticity during early morning hours, carryover effect of the drug in reducing muscle tone cannot be concluded from this study. To observe the carryover effect of the drug, further studies are required, regarding doses of drug, timing of drug administration, dosing schedule (single or divided doses).

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