Brief Communication

Efficacy and safety of rapid escalation of cabergoline in comparison to conventional regimen for macroprolactinoma: A prospective, randomized trial

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ABSTRACT

Introduction: Cabergoline (CAB) is conventionally started at a dose of 0.25-0.5 mg once a week with dose escalation at 1to 3months intervals. Previously, we and others have shown that rapid escalation and high doses of CAB can lead to normalization of serum PRL as early as 8.2 weeks in 93% of the patients. We hypothesize that rapid escalation of CAB doses, may help in both the earlier normalization of PRL and also significant shrinkage of tumor mass. **Study Design:** Randomized, prospective, interventional trial. **Subjects and Methods:** Forty two patients (male or female) with macroprolactinoma were randomized to conventional (group A) or rapid escalation (group B) of CAB dosing. In group B, CAB was started at a dose of 0.5 mg twice a week followed by a weekly hike of 1 mg/week, based on serum PRL and then monthly. The end point of the present study was a composite of normoprolactinemia and tumor shrinkage ≥50% from baseline. PRL and visual field analysis (weekly), other hormonal work up periodically and magnetic resonance imaging (sella) was performed monthly. **Results:** A total of 19 patients in each group completed a minimum follow-up of 6 months. There was a reduction of 72.7 ± 26.2% in group A and 84.1 ± 15.0 in group B (P = 0.24) within a week of CAB therapy. The duration of CAB treatment to normalize PRL was 10.2 ± 9.2 week(2-36) in group A and 7.2 ± 6.2 weeks(1-24) in group B (P = 0.28). There was no difference in the tumor shrinkage in either of the groups (92.3% [46.7-100%] in group A and 90.5% [66.6-100%] reduction in group B). The composite end point was achieved in 14 patients in group A (73.6%) and 16 patients in group B (84.2%) (P = 0.69). The composite end point was achieved in 13.1 ± 9.5 weeks (group A) versus 16.5 ± 14.1 weeks (group B) (P = 0.61). **Discussion:** This is first head to head comparative trial showing that a rapid hike of CAB dose is not associated with earlier normalization of PRL or reduction in tumor volume as compared to conventional monthly hike. There is no difference in the number of patients or duration required to achieve the composite end point. We obtained much earlier PRL normalization (8.4 weeks) as compared to previous studies (36-72 weeks), probably because PRL was not assessed as frequently as in the present study. Rapid escalation of CAB was well tolerated. **Conclusion:** A weekly or a conventional 4 weekly escalation of CAB have a similar efficacy with regards to the achievement of normoprolactinemia and significant tumor shrinkage for macroprolactinoma.

Key words: Rapid escalation, cabergoline, macroprolactinoma

Introduction

Prolactinomas are the most frequent pituitary tumor, and account for about 40% of all pituitary tumors. Cabergoline (CAB) is conventionally started at a dose of 0.5 mg once a week with dose escalation monthly and normoprolactinemia is achieved in 61-83% of macroprolactinoma with this regimen.[1] Previously, we and others have shown that rapid escalation and high doses of CAB can lead to normalization of serum PRL as early as 8.2 weeks in 93% of the patients and in almost all patients by 12 months.[2,3]

In macroprolactinoma, the aim of the treatment with dopamine agonists is not only to normalize Prolactin

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(PRL), but also the reduction in tumor size. However, none of the studies previously have considered both of these parameters as a composite end point of treatment. We conducted a randomized, prospective trial hypothesizing that rapid escalation of CAB doses, may help in both the earlier normalization of PRL and also significant shrinkage of tumor mass.

Subjects and Methods

Forty two patients (male or female) with drug naive macroprolactinoma were randomly allotted to the two treatment protocols. The end point was considered as a composite of normoprolactinemia and radiological evidence of tumor shrinkage ≥50% from baseline composite end point (CEP). CAB was started at a conventional dose of 0.5 mg once a week (group A) with a hike in doses every 4 weekly @ 0.5 mg/week based on PRL values until CEP was achieved. In rapid escalation (group B) group, CAB was started at a dose of 0.5 mg twice a week followed by a weekly hike of 1 mg/week, for the first 4 weeks followed by a monthly hike until CEP was achieved.

Serum PRL, estradiol and testosterone were done weekly for first 4 weeks and then 4 weekly until CEP. PRL was measured by electrochemiluminescenceimmunoassay sandwich method.Pituitary tumors were evaluated by a 3 Tmagnetic resonance imaging (MRI) scanner monthly till the 3rdmonth, and then 3 monthly until end point was achieved. Tumor volume was calculated by the Di Chiro and Nelson formula: volume = height × length × width × π/6. Visual field were assessed with automated perimeter weekly till 4 weeks and than 4 weekly until CEP was achieved.

Results

Forty two patients with macroprolactinoma were randomized to either of the two groups. However, 38 patients completed a minimum follow-up of 24 weeks (19 in each group). The baseline parameters in terms of age, gender, symptom duration, baseline prolactin levels, tumor volume, and duration of the follow-up were comparable. There was a reduction of 72.7 ± 26.2% (19.1-99.3%) (1901 ng/ml to 172.8 ng/ml) in group A and 84.1 ± 15.0 (45.5-99.5%) (2617 ng/ml to 227.0 ng/ml) in group B (P = 0.24) within a week of CAB therapy. Normoprolactinemia was achieved in 78.9 % (15 out of 19) and 84.2% (16 out of 19) patients by 10.2 ± 9.2 weeks(2-36) and 7.2 ± 6.2 weeks(1-24) (P = 0.28) in group A and B, respectively. The percentage reduction in PRL within1stweek correlated with 24 weeks PRL reduction (r = 0.6, P< 0.05).

There was significant tumor shrinkage by 51.6% (0-100%) in group A and 45.2% (13.0-97.6%) in group B (P = 0.45) as early as 4 weeks and an overall 92.3% (46.7-100%) in group A and 90.5% (66.6-100%) reduction in group B at the end of the follow-up. There was no difference in the tumor shrinkage in either of the groups. There was a positive correlation between tumor reduction at 4 weeks with 24 and 48-weeks tumor shrinkage (r = 0.60, P< 0.05; r = 0.53, P< 0.05, respectively). The CEP was achieved in 14 patients in group A (73.6%) and 16 patients in group B (84.2%) (P = 0.69). The duration of CAB therapy required to achieve CEP was 13.1 ± 9.5 weeks (group A) versus 16.5 ± 14.1 weeks (group B) (P = 0.61).The weekly dose of CAB required CEP was 1.3 ± 0.8 mg (0.5-3.0 mg) versus 4.2 ± 2.0 mg (1-9 mg) (P< 0.01) in two groups. receiver operating curve (ROC) curve analysis revealed that a 69.8% reduction in serum PRL within 1stweek had a specificity of 100% and sensitivity of 93.8% to achieve CEP with rapid escalation of CAB.

Discussion

This study shows that a rapid hike of CAB dose was not associated with earlier normalization of PRL or reduction in tumor volume as compared to conventional monthly hike in CAB doses. Moreover, there was no difference in the number of patients achieving the composite end point with either of the two regimens of CAB for the treatment of macroprolactinoma. Previously, two studies including ours have shown that rapid escalation of CAB is associated with earlier normalization of PRL;[2,3] however,none of the studies had a comparative group.

PRL normalization was much earlier in the present study in comparison to 19 weeks (73 % patients) and 24 weeks (82.1% patients) with 1-3 monthly escalation (conventional) of CAB[4]and 12 weeks (56.1% patients) and 24 weeks (80.7% patients) with a relatively rapid escalation (2 weekly).[3]This could be because previous studies have not assessed serum PRL as frequently as ours.

Tumor shrinkage was 76.2% over a period of 24 weeks, which is similar (66.8%) to our previous observation[2] and 88.6% by 72 weeks, which is similar but earlier than 92.1% reduction in tumor volume in 92.3% patients by Colao*etal.* over 3 years.[5]In some patients the prolactin and tumor reduction may not go hand in hand because of the dissociation between the anti-secretory and the anti-proliferative effect of the dopaminergic drugs.Therapy may need to be individualized depending on the prevailing symptoms. Similar observations have been made earlier, but the strategy of hiking the dose depending on tumor volume has not been practiced earlier.

The strengths of the study are that it is a randomized, prospective trial assessing two different regimen of CAB with a strategy to hike the dose until CEP was achieved in a homogenous group of drug naive patients with macroprolactinoma. This was a comprehensively designed study with frequent monitoring of serum PRL and MRI to delineate the natural history of response to CAB without any drop-outs.Rapid escalation of CAB is not superior to conventional dose escalation regarding duration to achieve, normoprolactinemia and tumor shrinkage. PRL and tumor volume reduction in initial 4 weeks correlates significantly with the further response to CAB with either of the dosing schedule.

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