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Botox in chronic migraine

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ABSTRACT

Objective: To review the evidence of efficacy of Botox in chronic migraine (CM), its critique and the key findings from prospective data on real life patients.

Development: CM is the most disabling form of migraine that affects around 2% of the general population and has significant impact on the quality of life of an individual with reduced ability to work or perform various activities of daily living. Medication used for prophylaxis of episodic migraine may well work in CM, although only topiramate has the published evidence. Botox was licensed for CM prophylaxis following publication of results of randomized controlled study (PREEMPT). Recently results of a large cohort of real life patients have been published (data from Hull Migraine Clinic, United Kingdom).

Conclusions: Hull Migraine Clinic study provides the first prospective real-life data on patients with CM treated with Botox in a tertiary headache centre. The study suggests a revision for defining a responder. The impact of medication overuse on the response, any predictors for response to treatment, long-term outcome, duration of treatment, development of resistance to Botox and relapse rate after stopping treatment remains unclear.

Key words. Botox. Chronic migraine. Chronic daily headaches. Migraine prophylaxis.

Botox en la migraña crónica

RESUMEN

Objetivo: Revisar la evidencia de la eficacia del Botox en la migraña crónica (MC), las críticas y los hallazgos claves a partir de los datos prospectivos de pacientes en la vida real.

Desarrollo: La MC es la forma más incapacitante de migraña, afecta aproximadamente al 2 % de la población general y tiene un impacto significativo en la calidad de vida del individuo con reducción de la capacidad para trabajar o ejecutar varias actividades de la vida diaria. El uso de los medicamentos para la profilaxis de la migraña episódica puede también servir para la MC, aunque solamente existe evidencia publicada sobre el topiramato. El Botox fue aprobado para la profilaxis de la migraña luego de la publicación de los resultados de un estudio controlado aleatorizado (PREEMPT). Recientemente los resultados de una cohorte amplia de pacientes en la vida real han sido publicados (datos de la Clínica de Migraña Hull, Reino Unido).

Conclusiones: El estudio de la Clínica de Migraña Hull brinda los primeros datos prospectivos de vida real en pacientes con MC tratados con Botox en un centro terciario de cefalea. Se sugiere una revisión de los criterios para definir la respuesta. Sin embargo, muchas preguntas permanecen por responder. El impacto del sobreuso de la medicación en la respuesta, de cualquiera de los predictores para la respuesta al tratamiento, el resultado a largo plazo, la duración del tratamiento, el desarrollo de resistencia al Botox y el ritmo de recaídas después de cesar el tratamiento permanecen sin aclarar.

Palabras clave. Botox. Cefalea crónica diaria. Migraña crónica. Profilaxis de la migraña.

INTRODUCTION

Chronic Migraine (CM) is the most disabling form of primary headache disorder with a prevalence of approximately 2% of the global population (1). The International Headache Society (IHS) defines CM as headaches of either tension-type or migraine-like for ≥15 days a month for at least 3 months of which ≥8 days per month fulfil criteria for either Migraine with or without aura or are relieved by triptan/ergot and may or may not be associated with analgesic overuse (2).

Around 50-80% of patients with CM seen in headache clinics overuse acute medications (3) and it remains uncertain whether the two entities are separate or complications of one another (4). In comparison to episodic migraine (<15 headache days/month) (2) patients with CM consume more healthcare resources (direct cost), are less likely to

work (indirect cost) and report poor health-related quality of life (HRQoL) (5). Co-morbidities like anxiety, depression and chronic pain are more prevalent in those with CM than non-CM sufferers (6,7).

Every patient with CM requires preventive treatment taken on a daily basis in addition to acute remedies to relieve pain during an attack. Preventive medications used in episodic migraine may also work in CM although a number of drugs (beta-blockers and tricyclic antidepressants) have been around for decades, are in-expensive and generic and are unlikely to have randomized controlled trial (RCT) data on their efficacy in CM. Topiramate remains the only medication to have established evidence in CM (8,9), although a significant number of patients report adverse events or lack of response that is also seen in other oral agents (e.g. sodium valproate, methysergide, pizotifen) (10).

Other treatments have limitations and drawbacks such as greater occipital nerve block (invasive and short term benefit), occipital nerve stimulator (costly and invasive). Emerging non-invasive neurostimulation devices such as transcranial magnetic stimulation and cefaly are promising, though in early stages with limited evidence of efficacy and lack long term data on its safety and cost-effectiveness (11).

The efficacy and safety of OnabotulinumtoxinA in adults with CM was established in the phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) study (12,13). The data lead to its approval in the UK by Medicine and Healthcare product Regulatory Agency (MHRA) in July 2010 (14) and in the USA by Food and Drug Administration (FDA) in October 2010 (15). Further appraisal by the National Institute for Health and Care Excellence (NICE) allowed its use within the National Health Service (NHS) in the UK (16).

CRITIQUE ON THE PREEMPT STUDY

Critics, leading experts in the field, reacted to these decisions with scepticism (17). It was argued that two third of patients treated in the PREEMPT study were overusing painkillers and may have pure medication overuse headache based on the 2nd edition of the International Classification on Headache Disorders (ICHD-II) (18). Moreover a third of patients in the PREEMPT study had previously received no prophylaxis which is interesting for a disabling condition. It was argued whether these patients could have been given oral treatments instead of Botox.

Another major criticism of the study was a high placebo response rate (35 %) and a difference of only 10 % between active and placebo groups. However, one could argue that injecting saline may not be comparable to placebo in oral trials as even dry injections may be considered active. Experts were also unconvinced on blinding in the study as facial expressions are likely to change with the muscular weakness, a well-known effect of Botox. However, if the blinding was not optimal, one would not have seen such a high placebo response in the study.

REAL LIFE DATA FROM CLINICAL PRACTICE

The evidence from a single, although large, study and with strong critique from the leading experts, the headache specialists and the funding authorities were keen to see whether the apparent benefit of Botox observed in the RCT translates into real life clinical practice. The cost of the drug was another limiting factor and commissioners wanted to be assured that they get value for their money. NICE, therefore, recommended its use when at least three oral preventive treatments had failed and medication overuse was appropriately addressed (16).

This prompted us to collect prospective data on all patients treated in our clinic with Botox and see if the results of the PREEMPT study could be replicated. Patients with medication overuse were included in the analysis similar to PREEMPT and recommendation by the International Headache Society (IHS) provided they are stratified accordingly (18).

The Hull Migraine Clinic (Hull Royal Infirmary and Spire Hospital Hull and East Riding) is one of the largest tertiary headache centres in the UK that sees 1200 new referrals per year from a large catchment area in the North of England. As patients were seen in the NHS we were obliged to follow the NICE guidelines with vast majority of patients offered Botox after they had failed three oral preventives. The data was collected using the headache diary (19) to capture the number of headache days, migraine days, and "crystal clear" days (we used the term “crystal clear” as many patients with mild headache would describe them headache free unless prompted). Assessment was also made on the days of analgesic medication use, triptan use, adverse events and days off work (if applicable). The quality of life (QoL) was assessed using the Headache Impact Test (HIT-6).

Patients were offered treatment based on a diary maintained for at least a month before treatment and were asked to continuously maintain the diary as a mandatory requirement for further treatment based on the response. For repeat treatments we followed the NICE criteria that defined responder as one with at least 30 % reduction in headache days

and stopped treatment if there was no response to two treatment cycles (negative stopping rule). However, we continued treatment until the patient had less than 10 headache days for at least three months rather than <15 days recommended by NICE as we felt that patients between 10-14 days of headaches are high frequency migraines and are more likely to relapse if the treatment was stopped (modified positive stopping rule).

It was noticed that a significant number of patients had marked reduction in the headache severity with improvement in HIT-6 score but no reduction in the number of headache days. Such patients were refused further treatment as they did not fulfil the NICE criteria and NHS funding. We felt reduction in migraine days were as an independent parameter of response and developed the Hull Criteria to define responder as one with at least 50 % reduction in either headache or migraine days or doubling of the "crystal clear" days provided they had at least three "crystal clear" days in the month before treatment. Those with less than three days had to achieve a minimum of 6 "crystal clear" days to be classed as responder (20).

Using Hull criteria two third of patients in our prospective data showed a meaningful response with 50 % reduction in headache days (32 %), 50 % reduction in migraine days (50 %) and increment in "crystal clear" days twice the base line (50 %). We concluded that assessment of migraine days and "crystal clear" days was more sensitive in evaluating response than headache days. There was significant reduction in consumption of pain-killers including triptans and improvement in productivity using days off work before and after treatment. The side effects were uncommon and mild. Around 15% complained of pain at the site of injection and neck stiffness and 11 % reported droopy eyes with full resolution of symptoms within 4 weeks.

Our prospective data from real life patients supports the outcome from PREEMPT study that Botox is an effective and safe treatment option as a prophylaxis in adult patients with CM. It has shown improvement in the QoL, reduced analgesic consumption and the number of headache and migraine days with increment in the number of "crystal clear" days after treatment. Our patient population is similar to what is seen in an average tertiary headache centre and in our opinion; other centres could see similar results from using Botox in their patients. The data in our study lacks an active comparator and we acknowledge that injectable treatments carry a high placebo response, although improvement in a number of measures including QoL suggests treatment related response.

Our patient population differed in some aspects to the PREEMPT patients. The patients in our cohort were more refractory migraineurs as 94.4% had previously failed three oral preventive compared to 35% in the PREEMPT study. Furthermore, the number of headache days before treatment in our population was much higher (27) than PREEMPT (19.9) although only 50 % of the cohort in our study were misusing painkillers compared to 67 % in the PREEMPT study.

CONCLUSIONS

Our study provides the first prospective real-life data on patients with CM treated with Botox in a tertiary headache centre. We feel that NICE criteria for defining responder need to be revisited in light of our data and recommend using the Hull criteria to evaluate response to treatment taking in to account the migraine and "crystal clear" days. We suggest that the stoppage rule in responders need to be revisited and treatment be continued until the patient has a low frequency migraine (<10 days). However, many questions remain to be answered. The impact of medication overuse on the response, any predictors for response to treatment, long-term outcome, duration of treatment, development of resistance to Botox and relapse rate after stoppage of treatment remains unclear. The data collection is ongoing and we expect to have some explanation to many uncertainties.

Conflicts of interest

The author declares no conflict of interests.

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Editor recommendation: another articles of F. Ahmed

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