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Letters to the Editor

Dear Sir,

With great interest we have read the article: 'Suboccipital injection with a mixture of rapid- and long-acting steroids in cluster headache: A double-blind placebo-controlled study' by Anna Ambrosini et al. in Pain 2005;118:92–6

In their article, the authors suggested an injection with a mixture of rapid- and long-acting betamethasone near the ipsilateral greater occipital nerve for the treatment of cluster headache. In their study they included patients with a known cluster headache period of 4 weeks or longer. Based on their results they concluded that suboccipital corticoid injections near the greater occipital nerve significantly reduced the cluster headache period compared to the normal expected length of the patients' cluster headache period.

Despite this remarkable efficacy of their therapeutic approach in cluster headache patients, we would like to comment on two aspects of their study:

At first we like to comment on the anatomical site of the injection they used in their study. The authors injected their solution halfway between the inion and the mastoid (3–4 cm below the inion) to reach the greater occipital nerve. The authors also stated that there is no standard recommendation for the precise location of the suboccipital injection. Vital et al. (1989) studied the course of 18 greater occipital nerves in 9 formalin embalmed adult cadavers (5 women and 4 men) and found that the greater occipital nerve crossed the trapezius muscle (where the nerve becomes subcutaneous) on average 31.8 mm from the midline and 22.2 mm below the external occipital protuberance. Ashkenazi and Levin (2004) also give an indication for the injection site of the greater occipital nerve. They locate the subcutaneous part of the greater occipital nerve 3.5 cm inferolaterally to the occipital protuberance. This position approximates the description by Vital JM et al. The spot where the greater occipital nerve becomes subcutaneous as described in Staubesand (1988) is not halfway between inion and mastoid but closer to the inion. Brown (1996) also locates the injection point closer to the inion. Based on these literature data we wonder whether the site of injection chosen by the authors is located near the greater occipital nerve. This is supported by the fact that the authors stated that there was no scalp numbness after they injected their solutions which contained Xylocaïne® 2% 0.5 ml. This could indicate that the injection site was not close enough to the greater occipital nerve or they used a too small amount of local anaesthetic. A larger amount of local anaesthetic, resulting in scalp anaesthesia, can confirm that their injection is close enough to the greater occipital nerve. Besides, they could have used a nerve stimulator to locate the greater occipital nerve. Because we question the right side of injection used in this study, the only conclusion to be drawn from their study is that an occipital subcutaneous injection of rapid- and long-acting betamethasone can prevent cluster headache attacks at the start of a cluster headache period.

Secondly, we have some concerns about the methodology of this study. To analyse the causality of the greater occipital nerve in the pathophysiology of cluster headache, an additional patient group should have been included where patients received a subcutaneous injection with betamethasone in another part of the body: this would allow to make a differentiation with a systemic therapeutic effect of the corticoids. Another striking feature was that 6 of the 11 positive responders to the injection with betamethasone and Xylocaïne® immediately became attack free. Of these 6 immediate responders 4 had a long-lasting effect. Since no patient in the placebo group had an immediate effect and since 4 patients had a long-lasting effect, the efficacy of their therapy neither can be attributed to the use of local anaesthetic nor to betamethasone since the observed effect occurred too quick after the injection. In our opinion this can be explained by two causes:

1. These patients were placebo responders although we admit it is odd that then there were no placebo responders in the placebo group.
2. The betamethasone and Xylocaïne® were injected intravascular.

To prove the role of the greater occipital nerve as part of the pathophysiology of cluster headache, it is our opinion that more randomised clinical trials are necessary where on one hand the proximity of the injection site near the greater occipital nerve needs to be confirmed and where on the other hand an extra control

group should be included where corticoids are injected in another part of the body to rule out a systemic corticoid effect. Due to the concerns expressed above we wonder if this study permits us to conclude that an injection with betamethasone near the greater occipital nerve is a valuable technique to treat cluster headache.

References

Vital JM, Grenier F, Dautheribes M, Baspeyre H, Lavignolle B, Sénégas J. An anatomic and dynamic study of the greater occipital nerve (n. of Arnold). Surg Radiol Anat 1989;11:205–10.

Ashkenazi A, Levin M. Three common neuralgias. Postgrad Med 2004;116:16–32.

Brown CR. Occipital neuralgia: symptoms, diagnosis and treatment. Pract Periodontics Aesthet Dent 1996;8:587–8.

Staubesand J. Sobotta Atlas of Human Anatomy. Munich – Vienna – Baltimore: Urban and Schwarzenberg; 1988.

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Response to Vanelderen et al.

We thank Drs. Vanelderen et al for their interest in our study of suboccipital steroid injections in the treatment of cluster headache. They criticise our study for the following reasons:

1. The injection site may not have reached the greater occipital nerve. This may be possible and we do not claim that the injection was hitting the GON, but that it was in the vicinity of the nerve. As mentioned in the methods section, we purposely performed deep injections in close contact with the occipital periosteum to avoid a known adverse effect of steroid injections, local alopecia (Shields et al., 2004). These injections do not target the GON at the site where it becomes subcutaneous as argued by Vanelderen, but at a deeper site where the nerve is more lateral (see Sobotta's Atlas). We agree that the injection did not produce numbness in most subjects probably because of the small amount of xylocaine (0.5 ml) and the fact that the GON was not directly injected.
2. Vanelderen et al. underscore a potential shortcoming of our study which we have discussed properly in the discussion section, i.e., is the therapeutic benefit mediated by a systemic effect of the steroid, and thus would a systemic injection be equally beneficial? As mentioned in the article, we hypothesise that the suboccipital site of injection is of importance for 2 reasons: first, for systemic administrations much higher doses of steroids are necessary to obtain an effect (Cianchetti et al., 1998; Mir et al., 2003) and, second, intramuscular injections of 120 mg prednisolone were found ineffective in one study (Anthony, 1987). However, we also state in the discussion section that the final proof has to come from a trial comparing suboccipital and sytemic steroid injections, which we are planning. Although initially considered, we decided not to add another treatment arm in the present study for logistic reasons and because recruitment of sufficient patients would have been problematic.
3. The immediate therapeutic response in the verum arm suggests, according to Vanelderen et al., that the patients were placebo responders or that the injection was intravascular. As a matter of fact (see results table), the response was immediate (no attacks after the injection) only in 4 out of 8 patients with a sustained response at 4 weeks and there was no correlation with the duration of longer-lasting remission. Nevertheless, it is clinically well documented (Anthony, 1987) that the attacks may disappear immediately after the injection in a subgroup of patients. As mentioned by Vanelderen et al. themselves this is unlikely to be a placebo effect, because it did not occur in the placebo arm. There is thus no need to speculate on an intravascular injection, the more so that this was excluded by proper aspiration before injecting the solutions and would have produced xylocaine-related side effects at least in some patients.

To conclude, we think that our injections were in the vicinity of the deeper, more proximal, portion of the greater suboccipital nerve and that our study demonstrates for the first time in a blinded placebo-controlled protocol that suboccipital steroid injections are indeed an effective treatment for epsiodic and chronic cluster headache, as claimed since a long time on empirical grounds. We agree that another comparative trial is necessary to demonstrate that systemic steroid injections are not equally effective.