Bupivacaine injection enlarges eye muscles

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ABSTRACT: We have injected bupivacaine (BUP) in volumes of 1.0 ml to 4.5 ml and in concentrations of 0.75% to 3.0% into the lateral rectus muscle (LR) of one eye in six adults with esotropia. At follow-up times of 30 to 190 days, alignment was improved by 0 to 25 prism diopters (pd) with enlargement of the injected portion of the LR on MRI images up to 53%. An overall enlargement of the superior rectus muscle (SR) of 34% and enlargement of individual muscle fibers in the injected area of 65% was seen in rabbits 28 days after injection. BUP injection appears to be a promising therapy for strabismus.

1 INTRODUCTION

Exposure to local anesthetics, especially those of the amino-amide class such as BUP, damages the muscle fibers of animals leaving the supporting cellular structures, nerves, and satellite cells intact (Benoit & Belt 1970, Bradley 1979, Park et al. 2004). Satellite cells proliferate and coalesce as new muscle fibers to repair this damage (Hall-Craggs 1980). In the fast muscle fibers of the rat limb muscles, actual hypertrophy then occurs (Rosenblatt 1990, Rosenblatt & Woods 1992, Plant et al. 2005). Eye muscles exposed to BUP inadvertently injected during retrobulbar anesthesia respond similarly with a resulting strabismus pattern of the eye deviated into the field of action of the enlarged muscle (Capo & Guyton 1996, Carboy & Jiang 1997, Hamed & Mancuso 1991). We reported the early result of BUP injection treatment in our first case (Scott et al. 2007). We now report follow-up on that case, the early results of BUP injection in five additional patients in this pilot study, and the results of BUP injection of the superior rectus muscle (SR) in rabbits.

2 METHODS

Standard clinical techniques were used for patient measurements. BUP was injected into the lateral rectus muscle using the electrical activity (EMG) recorded from the needle tip to guide the location of the injection. MRI scanning was done before injection to document the size of the muscles, obtaining 3.0 mm thick T1 coronal slices separated by 1.0 mm gaps through both orbits from the orbital apex to the equator of the eye, and axial slices through the horizontal muscles. Scanning was repeated 10 minutes after injection to show the location of the injected bolus, and again at about 60 days to show any change in the muscles. We used NIH public domain software *ImageJ* to make muscle size measurements and comparisons of the MRI images (Rasband 1997). Three rabbits were anesthetized. BUP was injected into the right SR under direct visualization through a conjunctival incision; saline marked with india ink was injected into the left SR. The animals were sacrificed at 28 days by anesthesia and perfusion, the muscles removed and weighed. The tissue was processed. On the cross-sections taken near the site of injection, a rectangular area equal on all sections and comprising about 1/3 of the total section area, was defined. The muscle fibers in this area were counted and their size measured using the BIOQUANT system (R&M Biometrics, Nashville, TN).

3 RESULTS

Table 1 summarizes the data of six injected patients. By chance all these cases were esotropic and thus the lateral rectus was injected. Percent enlargement is taken at the area of greatest change in the LR. Muscles were found to be locally enlarged, in the region of injection. Enlargement was calculated as follows. A post-injection coronal scan plane containing the enlarged region was identified, and the same orbital plane was selected in the pre-injection scan. The cross-sections of muscles in these corresponding planes were compared to yield "Enlargement" (Table 1). However, the post-injection eye tended to be more exotropic than the pre-injection eye, and so, the post-injection LR tended to be shorter. Assuming volume conservation, a muscle held at a shorter length would have larger cross-sections for this reason alone. Accounting for this effect gives "Corrected Enlargement" (Table 1).

Patient #3 was injected twice, with improvement each time. Patient #4 had a retrobulbar hemorrhage that may have displaced the BUP, thus explaining the lack of benefit. Patient #5 received a small volume and concentration, with no benefit. The pre-injection deviation of Patient #6 is the average of primary, 14pd ET; adduction, 20pd ET; abduction, 18pd ET; The post- injection deviation was 14pd ET in all positions.

The results of injection into the global layer of the SR in rabbit #2 are shown in fig 1. Rabbit #1, injected in lower dose into the global layer, and rabbit #3, injected into the superficial orbital layer, showed less change.

Table 1. Six patient results to present.

Patient	Deviation[1] (pd)	Deviation[2] (pd)	Follow-up[2] (day)	BUP Concentration (%)	BUP Volume (ml)	Enlargement (%)	Corrected Enlarge. (%)
1	14 E	4 E	190	0.75	4.5	59	53
2	10 E	4 E	36	3.0	1.5	17	14
3	25 E	16 E	161	1.5	1.0	44	39
(2nd Inj)	16 E	0 E	26	1.5	3.0	60	51
4	16 E	14 E	28	0.75	2.0	NA	NA
5	10 E	10 E	41	0.75	1.0	16	16
6	17 E	14 E	22	3.0	3.0	NA	NA

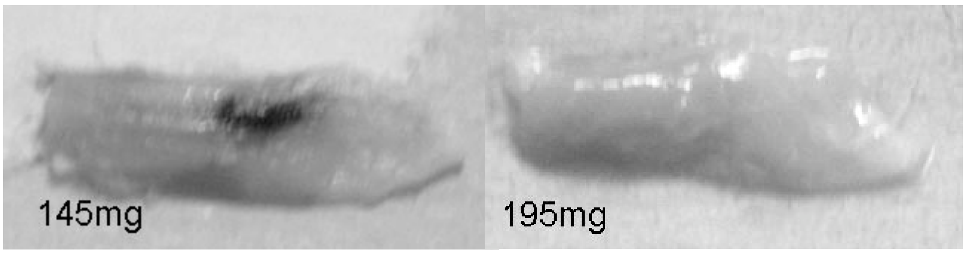

Figure 1. Rabbit #2, 28 days after injection; muscle insertions to the right. Left, control LSR, weight 145mg, injected with 0.5% saline marked with india ink mid-depth into the posterior muscle. Right, RSR, weight 195 mg, injected similarly with 0.5ml 3.0% bupivacaine. The size of individual global fibers (n=44) in the injected area of the RSR was increased by 65% over the size of global fibers (n=70) from the same region in the saline injected control LSR.

Figure 2. Patient #3, left, pre-injection 25pd ET, middle, day 26, 16pd ET, right, day 187 with second injection on day 161, 0pd ET.

4 DISCUSSION

The clinical cases had an increase of deviation of several degrees immediately after injection, recovering to the original alignment in 7-10 days, with some cases improving up to 30 days after injection. Probably a valid clinical assessment of effect can be made at 30-40 days. Large volumes seem to give a better effect. The longest followed result, an alignment change of 10 pd which has persisted over 190 days, came from an injection of 4.5 ml of 0.75% BUP; the worst result, no change, came from and injection of 1.0 ml of 0.75% BUP. Strabismus as an inadvertent effect of retro-orbital injection occurred with increasing frequency as the injection volume increased (Goldchmit and Scott 1994). MRI images show that injection of 3.0 ml fills the muscle if placed perfectly. Placement of the injection in the posterior portion of the muscle seems to be important, as the fluid tends to extend forward after injection. When placing the needle in the muscle at what seemed clinically a very posterior level, subsequent MRI images show that it should have been 8-10 mm more posterior. With EMG to guide the needle position, posterior placement should hold no hazard. The lateral rectus is rarely affected in wayward retro-orbital injections. If this represents a lower sensitivity of the lateral rectus to BUP, then larger angular deviation changes may result from injection of other muscles. We made one re-injection at 161 days after the first injection with good effect (see fig 2), but the optimum time for re-injection remains undefined.
Enlargement of the muscle and of the global fibers of the BUP-injected SR of the rabbit is encouraging, as the first report of eye muscle injection of BUP in the rabbit (Park et al. 2004) showed effects in the orbital layer only.

Greater deviation correction in abduction and adduction than straight ahead was seen in several patients. This mirrors the strabismus pattern seen after retro-orbital injections (Capo & Guyton 1996). The modeling program Orbit 1.8™ (Miller et al. 1999) indicates that only muscle hypertrophy can explain the pattern of increased deviation into abduction characteristic of these cases (overaction), with increased elastic stiffness explaining the restriction to adduction. Muscle shortening from sarcomere adaptation is the likely explanation for long lasting deviation change (Scott 1994). Fibrosis and scarring as causes for such strabismus have never been documented by biopsy in humans, nor found in the dozens of animal injection studies. Measurement of eye muscle sizes, forces, and changes in alignment are underway in animals and humans in order to define the optimum injection volume, drug concentration, and injection placement in the muscle.

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