**Supplementary Table 1:** Postoperative results after combining groups that received Prednisolone and NSAID and groups that received NSAID monotherapy

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pred+NSAID** | **NSAID** | **Drop-less** |
| **Anterior chamber flare** |  |  |  |
| Baseline, median [CI] | |-------------------------------- 10.1 [9.7 ; 10.6] --------------------------------| | | |
|  |  |  |  |
| Three days postop,  median [CI] | 17.8 [16.4 ; 19.3] | 20.1 [18.5 ; 21.8] | 30.4 [27.0 ; 34.2] |
|  |  |  |  |
| Change relative to control,  median [CI] | Control | 1.128 [1.009 ; 1.261] | 1.708 [1.486 ; 1.963] |
| p-value/adj-p-value |  | 0.0340 / 0.0850 | <0.0001 / <0.0001 |
|  |  |  |  |
| **Cells in anterior chamber** |  |  |  |
| Three days postop,  mean [CI] | 3.6 [3.3 ; 4.0] | 4.1 [3.6 ; 4.5] | 5.5 [4.5 ; 6.6] |
|  |  |  |  |
| Difference from control,  mean [CI] | Control | 0.4 [-0.2 ; 1.0] | 1.9 [0.8 ; 3.0] |
| p-value/adj-p-value |  | 0.1695 / 0.3710 | 0.0009 / 0.0028 |
|  |  |  |  |
| **Intraocular pressure** |  |  |  |
| Baseline, mean [CI] | |-------------------------------- 14.3 [13.9 ; 14.6] -------------------------------| | | |
|  |  |  |  |
| Three days postop,  mean [CI] | 13.5 [13.0 ; 13.9] | 12.3 [11.9 ; 12.7] | 11.1 [10.7 ; 11.5] |
|  |  |  |  |
| Difference from control,  mean [CI] | Control | -2.2 [-2.8 ; -1.6] | -3.1 [-3.9 ; -2.4] |
| p-value/adj-p-value |  | <0.0001 / <0.0001 | <0.0001 / <0.0001 |
|  |  |  |  |
| **Visual acuity** |  |  |  |
| Baseline, mean [CI] | |-------------------------------- 0.29 [0.28 ; 0.30] --------------------------------| | | |
|  |  |  |  |
| Three days postop,  mean [CI] | 0.10 [0.07 ; 0.12] | 0.08 [0.06 ; 0.11] | 0.11 [0.07 ; 0.14] |
|  |  |  |  |
| Difference from control,  mean [CI] | Control | -0.02 [-0.05 ; 0.02] | 0.01 [-0.03 ; 0.05] |
| p-value/adj-p-value |  | 0.3186 / 0.6105 | 0.5722 / 0.8545 |

Estimates regarding anterior chamber flare, intraocular pressure and visual acuity were derived from the constrained linear mixed model with inherent baseline adjustment. For cells in anterior chamber, comparisons with control were made with Welch' two-sample t-test. Flare is presented as photons per millisecond, intraocular pressure is presented as mmHg and visual acuity is presented in logMAR. CI = 95% confidence interval. Adj-p-value = false discovery rate (FDR) adjusted p-value.

**Supplementary Table 2:** Postoperative results after combining eye drop groups that received prophylactic treatment three days before surgery (Pre-operative) and groups that received prophylactic treatment on the day of surgery (Post-operative)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Pre-operative** | **Post-operative** | **Drop-less** |
| **Anterior chamber flare** |  |  |  |
| Baseline, median [CI] | |-------------------------------- 10.1 [9.7 ; 10.6] --------------------------------| | | |
|  |  |  |  |
| Three days postop,  median [CI] | 19.0 [17.5 ; 20.6] | 18.8 [17.3 ; 20.4] | 30.4 [27.0 ; 34.2] |
|  |  |  |  |
| Change relative to control,  median [CI] | Control | 0.991 [0.886 ; 1.108] | 1.601 [1.391 ; 1.842] |
| p-value/adj-p-value |  | 0.8673 / 1.0 | <0.0001 / <0.0001 |
|  |  |  |  |
| **Cells in anterior chamber** |  |  |  |
| Three days postop,  mean [CI] | 3.8 [3.3 ; 4.2] | 3.9 [3.5 ; 4.3] | 5.5 [4.5 ; 6.6] |
|  |  |  |  |
| Difference from control,  mean [CI] | Control | 0.1 [-0.5 ; 0.7] | 1.8 [0.6 ; 2.9] |
| p-value/adj-p-value |  | 0.6575 / 0.9139 | 0.0029 / 0.0081 |
|  |  |  |  |
| **Intraocular pressure** |  |  |  |
| Baseline, mean [CI] | |-------------------------------- 14.3 [13.9 ; 14.6] -------------------------------| | | |
|  |  |  |  |
| Three days postop,  mean [CI] | 12.5 [12.0 ; 13.0] | 11.6 [11.2 ; 12.0] | 10.9 [10.5 ; 11.2] |
|  |  |  |  |
| Difference from control,  mean [CI] | Control | -0.3 [-0.9 ; 0.3] | -2.2 [-3.0 ; -1.4] |
| p-value/adj-p-value |  | 0.3428 / 0.6366 | <0.0001 / <0.0001 |
|  |  |  |  |
| **Visual acuity** |  |  |  |
| Baseline, mean [CI] | |-------------------------------- 0.29 [0.28 ; 0.30] --------------------------------| | | |
|  |  |  |  |
| Three days postop,  mean [CI] | 0.08 [0.06 ; 0.11] | 0.10 [0.07 ; 0.12] | 0.11 [0.07 ; 0.14] |
|  |  |  |  |
| Difference from control,  mean [CI] | Control | 0.01 [-0.02 ; 0.04] | 0.03 [0.00 ; 0.06] |
| p-value/adj-p-value |  | 0.4534 / 0.7423 | 0.2075 / 0.4385 |

Estimates regarding anterior chamber flare, intraocular pressure and visual acuity were derived from the constrained linear mixed model with inherent baseline adjustment. For cells in anterior chamber, comparisons with control were made with Welch' two-sample t-test. Flare is presented as photons per millisecond, intraocular pressure is presented as mmHg and visual acuity is presented in logMAR. CI = 95% confidence interval. Adj-p-value = false discovery rate (FDR) adjusted p-value.

**Supplementary Table 3:** Best case control

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pred+NSAID-Pre** | **Pred+NSAID-Post** | **NSAID-Pre** | **NSAID-Post** | **Drop-less** |
| **Anterior chamber flare** |  |  |  |  |  |
| Baseline, median [CI] | |-------------------------------------------- 10.1 [9.7 ; 10.6] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, median [CI] | 17.3 [15.4 ; 19.4] | 18.6 [16.6 ; 20.9] | 21.1 [18.8 ; 23.7] | 20.2 [18.0 ; 22.7] | 31.3 [27.9 ; 35.1] |
|  |  |  |  |  |  |
| Change relative to control, median [CI] | Control | 1.075  [0.881 ; 1.313] | 1.218  [0.995 ; 1.490] | 1.167  [0.955 ; 1.427] | 1.807  [1.476 ; 2.213] |
| p-value |  | 0.3625 | 0.0148 | 0.0548 | < 0.0001 |
|  |  |  |  |  |  |
| **Cells in anterior chamber** |  |  |  |  |  |
| Three days postop, mean [CI] | 3.3 [2.9 ; 3.8] | 3.9 [3.4 ; 4.4] | 4.2 [3.4 ; 5.0] | 4.0 [3.5 ; 4.6] | 5.6 [4.7 ; 6.6] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | 0.6 [-0.1 ; 1.2] | 0.9 [-0.1 ; 1.8] | 0.7 [0.0 ; 1.4] | 2.3 [1.2 ; 3.4] |
| p-value |  | 0.1122 | 0.0646 | 0.0462 | < 0.0001 |
|  |  |  |  |  |  |
| **Intraocular pressure** |  |  |  |  |  |
| Baseline,  mean [CI] | |-------------------------------------------- 14.3 [13.9 ; 14.6] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, mean [CI] | 13.4 [12.7 ; 14.0] | 13.6 [13.0 ; 14.2] | 11.6 [11.0 ; 12.3] | 11.2 [10.6 ; 11.9] | 10.8 [10.1 ; 11.4] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | 0.2 [-0.7 ; 1.1] | -1.7 [-2.6 ; -0.9] | -2.1 [-3.0 ; -1.3] | -2.6 [-3.5 ; -1.7] |
| p-value |  | 0.6825 | 0.0001 | < 0.0001 | < 0.0001 |
|  |  |  |  |  |  |
| **Visual acuity** |  |  |  |  |  |
| Baseline, mean [CI] | |-------------------------------------------- 0.29 [0.28 ; 0.31] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, mean [CI] | 0.10 [0.06 ; 0.13] | 0.10 [0.07 ; 0.14] | 0.07 [0.04 ; 0.11] | 0.10 [0.07 ; 0.14] | 0.12 [0.09 ; 0.16] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | 0.01 [-0.04 ; 0.05] | -0.02 [-0.07 ; 0.02] | 0.01 [-0.04 ; 0.05] | 0.03 [-0.02 ; 0.07] |
| p-value |  | 0.7476 | 0.3203 | 0.7481 | 0.2591 |

Analysis where missing values in the control group were substituted with the 10th percentile and missing values of the remaining groups were substituted with the 90th percentile of the observed data. Estimates regarding anterior chamber flare, intraocular pressure and visual acuity were derived from the constrained linear mixed model with inherent baseline adjustment. For cells in anterior chamber, comparisons with control were made with Welch' two-sample t-test. Flare is presented as photons per millisecond, intraocular pressure is presented as mmHg and visual acuity is presented in logMAR. CI = 95% confidence interval.

**Supplementary Table 4:** Worst case control

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pred+NSAID-Pre** | **Pred+NSAID-Post** | **NSAID-Pre** | **NSAID-Post** | **Drop-less** |
| **Anterior chamber flare** |  |  |  |  |  |
| Baseline, median [CI] | |-------------------------------------------- 10.1 [9.7 ; 10.6] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, median [CI] | 18.2 [16.2 ; 20.4] | 17.8 [15.9 ; 19.9] | 20.1 [17.9 ; 22.5] | 19.2 [17.2 ; 21.6] | 28.3 [25.1 ; 31.9] |
|  |  |  |  |  |  |
| Change relative to control, median [CI] | Control | 0.977  [0.797 ; 1.196] | 1.103  [0.899 ; 1.355] | 1.058  [0.863 ; 1.298] | 1.557  [1.267 ; 1.913] |
| p-value |  | 0.7696 | 0.2303 | 0.4860 | < 0.0001 |
|  |  |  |  |  |  |
| **Cells in anterior chamber** |  |  |  |  |  |
| Three days postop, mean [CI] | 3.5 [3.1 ; 4.0] | 3.8 [3.3 ; 4.3] | 4.1 [3.3 ; 4.9] | 3.9 [3.4 ; 4.4] | 5.2 [4.2 ; 6.3] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | 0.3 [-0.4 ; 1.0] | 0.5 [-0.4 ; 1.5] | 0.4 [-0.3 ; 1.1] | 1.7 [0.6 ; 2.8] |
| p-value |  | 0.4057 | 0.2536 | 0.2907 | 0.0028 |
|  |  |  |  |  |  |
| **Intraocular pressure** |  |  |  |  |  |
| Baseline, mean [CI] | |-------------------------------------------- 14.3 [13.9 ; 14.6] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, mean [CI] | 13.7 [13.1 ; 14.3] | 13.3 [12.6 ; 13.9] | 11.3 [10.7 ; 12.0] | 10.9 [10.3 ; 11.6] | 10.1 [9.5 ; 10.8] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | -0.4 [-1.3 ; 0.4] | -2.4 [-3.2 ; -1.5] | -2.8 [-3.6 ; -1.9] | -3.6 [-4.4 ; -2.7] |
| p-value |  | 0.3311 | < 0.0001 | < 0.0001 | < 0.0001 |
|  |  |  |  |  |  |
| **Visual acuity** |  |  |  |  |  |
| Baseline, mean [CI] | |-------------------------------------------- 0.29 [0.28 ; 0.31] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, mean [CI] | 0.11 [0.07 ; 0.14] | 0.09 [0.06 ; 0.12] | 0.06 [0.03 ; 0.10] | 0.09 [0.06 ; 0.13] | 0.10 [0.06 ; 0.13] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | -0.02 [-0.06 ; 0.03] | -0.05 [-0.09 ; -0.00] | -0.02 [-0.06 ; 0.03] | -0.01 [-0.05 ; 0.04] |
| p-value |  | 0.4053 | 0.0459 | 0.5145 | 0.7170 |

Analysis where missing values in the control group were substituted with the 90th percentile and missing values of the remaining groups were substituted with the 10th percentile of the observed data. Estimates regarding anterior chamber flare, intraocular pressure and visual acuity were derived from the constrained linear mixed model with inherent baseline adjustment. For cells in anterior chamber, comparisons with control were made with Welch' two-sample t-test. Flare is presented as photons per millisecond, intraocular pressure is presented as mmHg and visual acuity is presented in logMAR. CI = 95% confidence interval.

**Supplementary Table 5:** Analyses without extreme outliers.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Pred+NSAID-Pre** | **Pred+NSAID-Post** | **NSAID-Pre** | **NSAID-Post** | **Drop-less** |
| **Cells in anterior chamber** |  |  |  |  |  |
| Three days postop, mean [CI] | 3.4 [3.0 ; 3.9] | 3.7 [3.3 ; 4.1] | 3.8 [3.4 ; 4.2] | 3.8 [3.4 ; 4.3] | 4.6 [4.0 ; 5.3] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | 0.3 [-0.3 ; 0.9] | 0.4 [-0.3 ; 1.0] | 0.4 [-0.2 ; 1.1] | 1.2 [0.4 ; 2.0] |
| p-value |  | 0.3836 | 0.2419 | 0.2002 | 0.0034 |
|  |  |  |  |  |  |
| **Visual acuity** |  |  |  |  |  |
| Baseline, mean [CI] | |-------------------------------------------- 0.29 [0.27 ; 0.30] --------------------------------------------| | | | | |
|  |  |  |  |  |  |
| Three days postop, mean [CI] | 0.09 [0.06 ; 0.12] | 0.09 [0.06 ; 0.13] | 0.07 [0.04 ; 0.10] | 0.10 [0.07 ; 0.13] | 0.11 [0.08 ; 0.14] |
|  |  |  |  |  |  |
| Difference from control, mean [CI] | Control | 0.00 [-0.04 ; 0.04] | -0.03 [-0.04 ; 0.03] | 0.01 [-0.04 ; 0.05] | 0.02 [-0.03 ; 0.06] |
| p-value |  | 0.9314 | 0.2586 | 0.8254 | 0.4481 |

*Number of cells > 14 and visual acuity > 0.80 logMAR were removed. Estimates regarding visual acuity were derived from the constrained linear mixed model with inherent baseline adjustment. For cells in anterior chamber, comparisons with control were made with Welch' two-sample t-test. Visual acuity is presented in logMAR. CI = 95% confidence interval.*

**Supplementary Table 6:** Analysis for post randomization confounding.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Baseline** | **P-value** |  | **Three days postop** | **P-value** |
| **Anterior chamber flare** |  |  |  |  |  |
| Relative effect of allocation to Pred+NSAID-Pre,  median [CI] | --------------------| | |  | 1.874 [1.001 ; 3.508] | 0.0495 |
|  |  |  |  |
| Relative effect of allocation to Pred+NSAID-Post,  median [CI] |  | 1.899 [1.017 ; 3.545] | 0.0440 |
|  |  |  |  |
| Relative effect of allocation to NSAID-Pre,  median [CI] | N/A | |  | 2.226 [1.203 ; 4.119] | 0.0109 |
|  | |-------------------- | |  |  |  |
| Relative effect of allocation to NSAID-Post,  median [CI] |  | 2.089 [1.121 ; 3.895] | 0.0205 |
|  |  |  |  |
| Relative effect of allocation to Drop-less,  median [CI] |  | 3.293 [1.777 ; 6.105] | 0.0002 |
|  |  |  |  |  |  |
| Relative effect of increasing age by 1 year,  median [CI] | 1.013 [1.006 ; 1.020] | 0.0002 |  | 0.998 [0.989 ; 1.006] | 0.5935 |
|  |  |  |  |  |  |
| Relative effect of being male,  median [CI] | 1.113 [1.013 ; 1.223] | 0.0258 |  | 1.015 [0.901 ; 1.142] | 0.8112 |
|  |  |  |  |  |  |
| Relative effect of doubling CDE,  median [CI] | 0.981 [0.925 ; 1.040] | 0.5126 |  | 1.029 [0.955 ; 1.108] | 0.4539 |

*Estimates were derived from the constrained linear mixed model with inherent baseline adjustment. CDE = cumulative dissipated energy (“phaco energy”). N/A = no estimate available. CI = 95% confidence interval.*