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1 **Intravitreal gas for symptomatic vitreomacular adhesion: a synthesis of the literature**

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25 **PURPOSE:** Symptomatic vitreomacular adhesion (svMA) is defined as visual loss secondary to foveal
26 damage from vitreomacular traction (VMT), and includes isolated VMT, impending macular hole, and
27 full-thickness macular hole with persisting vitreous attachment. Management options include pars
28 plana vitrectomy, intravitreal ocriplasmin, intravitreal gas injection or observation. This synthesis of
29 the literature aimed to assess the safety and efficacy of intravitreal gas for svMA.

30 **METHODS:** Articles describing patients with VMT or macular hole treated with intravitreal expansile
31 gas were selected by systematic literature review using MEDLINE, EMBASE, and the Cochrane
32 Database of Controlled Trials (CENTRAL) up to September 2016. The main outcomes at 1 month and
33 final review were logarithm of the minimum angle of resolution (logMAR) visual acuity (VA),
34 anatomical success (absence of both VMT and macular hole, without pars plana vitrectomy), and
35 adverse events. The intended comparator was observation.

36 **RESULTS:** Nine of 106 identified articles were eligible and none were randomized controlled trials.
37 The mean VA of 91 eyes improved from 0.55 (6/21) to 0.48 (6/18) at 1 month and 0.35 (6/13) at final
38 review. The mean VA at final review, prior to a vitrectomy, was 0.42 (6/16). Anatomic success was
39 48% at 1 month and 57% at final review. The reported adverse events comprised retinal detachment
40 in two highly myopic eyes.

41 **CONCLUSION:** Intravitreal gas injection can relieve svMA. Larger controlled studies are needed to
42 determine safety and efficacy relative to observation, ocriplasmin, or vitrectomy.

43 **Key Words:** Gas, Macula, Vitreomacular adhesion, Vitreomacular traction, Vitreous

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47 **Introduction**

48 Perifoveal vitreous separation may occur as part of normal ageing, or as part of a disease spectrum
49 ranging from vitreomacular traction (VMT) to macular hole (MH). Symptomatic vitreomacular
50 adhesion (svMA) is defined as visual loss secondary to foveal damage as a result of VMT, and
51 includes isolated VMT, impending MH, and full thickness MH with persisting vitreous attachment
52 (Jackson et al. 2013; Simpson et al. 2012).

53 Treatment strategies for VMA depend on disease severity. Asymptomatic VMT can be observed,
54 since vitreofoveal separation may occur spontaneously without sequelae. However, persisting VMT
55 may result in foveal damage, thus prompting treatment if symptoms are significant or visual acuity
56 (VA) is reduced (Hikichi et al. 1995; Melberg et al. 1995; Sonmez et al. 2008). For many years, pars
57 plana vitrectomy (PPV) was the standard approach for VMT (Steel & Lotery 2013). More recently,
58 pharmacological vitreolysis with ocriplasmin (Jetrea; Thrombogenics, Leuven, Belgium) has emerged
59 as an alternative that may avoid the need for PPV (Benz et al. 2010; De Smet et al. 2009; Maier et al.
60 2015; Stalmans et al. 2010; Stalmans et al. 2012; Gandorfer 2008; Jetrea Summary of Product
61 Characteristics 2013; NICE technology appraisal guidance 2013).

62 Another treatment modality for svMA is pneumatic displacement with an intravitreal expansile gas
63 bubble, potentially avoiding the need for vitrectomy or enzymatic vitreolysis. The potential
64 advantage of an intravitreal gas injection includes its low cost and ease of adoption. For example,
65 the cost of ocriplasmin and vitrectomy are estimated at \$3 950 (jetrea.com/JETRAOrderinginfo.pdf)
66 and \$3 147 in the USA, respectively, and £3 000 and £1 634, respectively, in the UK (Gupta et al.
67 2008; Nicod et al. 2016). The cost of ocriplasmin is magnified by the fact that many cases fail to
68 respond and therefore still need to progress to vitrectomy. Gases such as C₃F₈ and SF₆ cost as little as
69 £1 if taken from large medical gas cylinders, or typically less than £100 from single use canisters
70 licensed for intraocular use. Intravitreal gas is easy to store and administer, and does not require the

71 capital costs or surgical expertise needed to undertake PPV. In addition, intravitreal gas injection
72 may potentially be a safer procedure compared to the more invasive PPV.

73 Given these potential advantages of intravitreal gas we undertook a review of the safety and efficacy
74 of intravitreal gas for sVMA, to guide clinical care or future studies. Specifically, we aimed to
75 determine the benefit of intravitreal gas in terms of releasing VMT or closing MHs, the effect on VA,
76 and the risk in terms of intra- and postoperative complications.

77 **Materials and Methods**

78 *Eligibility criteria for considering studies for this review*

79 The population was patients with sVMA, namely VMT with or without MH, to include stage 1, 2 and
80 3 MH. The intervention was a single intravitreal expansile gas injection. The intended control was
81 natural history. The main efficacy outcomes were VA and anatomic success, defined as an absence
82 of VMT or MH without recourse to PPV. Both outcomes were assessed at 1 month and final follow
83 up. Safety outcomes included all reported surgical complications or adverse events attributed to
84 intravitreal gas. The study protocol was registered with the international prospective register of
85 systematic reviews (2015:CRD42015017338, National Institute of Health Research Centre for
86 Reviews and Dissemination, University of York, UK) and conducted in accordance with Preferred
87 Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance ([http://www.prisma-
88 statement.org/](http://www.prisma-statement.org/), accessed 28 May 2015).

89 There were no restrictions with regards to gender or ethnicity of patients or language of article. In
90 the anticipated absence of any randomized controlled trials and to maximise safety data,
91 prospective, retrospective, controlled and uncontrolled studies, including case reports, were eligible.
92 Inclusion criteria were: studies of VMT or stage 1-3 MHs (Gass 1988); at least 28 days follow up; VA
93 outcomes reported; either MH closure or VMT release rates; reporting results in adults over 18 years
94 of age. We excluded editorials and expert opinions, and articles appearing as abstract only. Eyes with

95 prior treatment of VMA were excluded, including PPV, intravitreal gas, and pharmacologic
96 vitreolysis. Eyes being treated for myopic macular hole retinal detachment were excluded.

97 *Search methods for identifying studies*

98 PubMed MEDLINE, EMBASE, and Cochrane Database of Controlled Trials (CENTRAL) searches were
99 performed including all articles up to and including September 2016 using Boolean operators with
100 the following keywords (and corresponding MESH headings if they were available): SF6, sulfur
101 hexafluoride, sulphur hexafluoride, C2F6, hexafluoroethane, C3F8, octafluoropropane,
102 perfluoropropane, gas, intravitreal, macular hole, sulphur hexafluoride, vitreomacular adhesion, and
103 vitreomacular traction. An example search is show in Appendix 1.

104 *Study Selection*

105 Abstracts were retrieved from the search and further articles were identified in the reference lists of
106 the retrieved articles. Two clinicians (JN and TJ) independently assessed articles for provisional
107 eligibility based on their abstract. Full-text copies of all possibly relevant manuscripts were obtained,
108 to determine final eligibility. Any discrepancy in eligibility was resolved by consensus following
109 discussion.

110 *Data collection and risk of bias assessment*

111 Two reviewers (JN and TJ) extracted the relevant information into a database, including: 1) overview
112 of the study (aim and key findings); 2) methodological details (study design, study population,
113 inclusion criteria, exclusion criteria, intervention, comparator if available, study period); 3) VA before
114 and after gas; 4) anatomic success after gas; 5) need for vitrectomy; 6) safety outcomes. To compare
115 across studies, VA was converted to logarithm of the minimum angle of resolution (logMAR) units
116 (Jackson et al. 2013).

117 *Data synthesis and analysis*

118 Where necessary, authors were contacted to obtain unpublished raw data. Two-sided, paired t-tests
119 were used to compare mean VA before and after interventions. Safety was assessed by adverse
120 events (AEs) and serious adverse events (SAEs) reported. Safety data were pooled across all studies,
121 using individual data where available or study means otherwise. Sub-group analysis was performed
122 for those with diagnoses of MH or VMT.

123 **Results**

124 Of 106 articles, 106 abstracts were assessed as potentially eligible, from which nine articles were
125 deemed eligible after full text review. A total of 91 eyes from 90 patients with sVMA were included
126 from one non-randomized controlled study, seven uncontrolled studies and two individual case
127 reports (Table 1) (Chan et al. 1995; Costa et al. 2001; Chen et al. 2012; Jorge et al. 2006; Mori et al.
128 2007; Gupta & McHugh 2011; Rodrigues et al. 2013; Day et al. 2016; Yu et al. 2016). Additional,
129 anonymous participant-level VA data were obtained from one study author as this information was
130 not available in his report, in accordance with PRISMA guidance (Rodrigues et al. 2013). A risk of bias
131 tool was not used as the literature search found no eligible randomised controlled trials.

132 (Table 1 Position)

133 There were 24 males and 59 females, with a mean age of 67.3 years (range 36 to 91, n = 85). Gender
134 and age data were missing from one study of six eyes and the gender of a patient was not stated in
135 one case report. There were 44 eyes (44 patients) with a baseline diagnosis of VMT, including 14
136 with stage 1 MH. Stage 2 MH was present in 45 eyes (45 patients), and stage 3 MH in 2 eyes (2
137 patients). One patient underwent bilateral treatment for a stage 3 MH in the right eye and a stage 2
138 MH in the left eye. Perfluoropropane gas was used in 62 eyes, with the volume injected varying from
139 0.2ml to 0.5ml. Sulphur hexafluoride 0.5 ml was used in the other 29 eyes. Post-operative posturing
140 techniques were not consistent between studies, varying from 14 days of face down posturing to no
141 posturing. A PPV was performed in 31 of 91 eyes (34%) for varying reasons: persisting MH despite

142 VMT release with gas in 14 eyes (45%), persisting VMT and MH despite gas injection in eleven eyes
143 (36%), retinal detachment in two eyes (7%), new MH following successful VMT release with gas in
144 two eyes (7%), persisting isolated VMT in one eye (3%) and vitreous haemorrhage secondary to
145 proliferative diabetic retinopathy in one eye (3%).

146 At 1 month following gas injection, 44 of 91 eyes (48%) had anatomic success, defined as no VMT or
147 MH and without recourse to PPV. At a mean final follow up period of 14.5 months (range: 1 to 48
148 months), anatomic success was achieved in 52 eyes (57%). Twenty six eyes underwent PPV
149 specifically for failure of gas, 14 for persisting MH, 11 for persisting combined VMT/MH, 1 for
150 persisting isolated VMT, and all responded with anatomic success.

151 The mean pre-intervention logMAR VA was 0.55 (n = 91; range: 0 to 2.00; Snellen equivalent 6/21).

152 In the 62 eyes (68%) with VA documented at 1 month the mean VA improved from 0.57 logMAR by
153 0.09 units to 0.48 logMAR (range: 0 to 2.00; 6/18; p=0.036). No eyes had undergone PPV by month
154 1. Mean VA at final follow up was 0.35 logMAR (n = 88; range: -0.09 to 2.00; 6/13), which was
155 significantly better than baseline (p<0.001)(Table 2). A post hoc analysis of the final VA outcome
156 prior to any PPV revealed a VA of 0.42 logMAR (n=78; 6/16), significantly better than baseline
157 (p=0.001). Three patients did not have a post-gas VA documented.

158 (Table 2 position)

159 In the 30 eyes (33%) with a baseline diagnosis of isolated VMT, the mean VA was 0.55 logMAR
160 (range: 0.1 to 2.00; 6/21) at baseline and remained unchanged at 0.55 (range: 0.00 to 2.00; 6/21) at
161 month 1 (n = 22; p=0.226), before subsequently improving to 0.49 (range: 0.00 to 2.00; 6/19) at a
162 mean follow up of 7.7 months (n=28; p = 0.096) (Figure 1). Anatomic success was achieved in
163 fourteen eyes (47%) at month 1 and eighteen eyes (60%) at final follow up (Figure 2). Eight of 30
164 (27%) eyes with VMT underwent PPV, all after month 1. The indication in one case was vitreous
165 haemorrhage secondary to proliferative diabetic retinopathy in which the initial gas injection had

166 previously resulted in a complete posterior vitreous detachment (PVD) at month 1. In two eyes, PPV
167 was performed for a full-thickness MH following earlier successful VMT release with gas. The other
168 five PPVs were carried out to treat persistent VMT despite intravitreal gas injection.

169 A stage 1 MH was present at baseline in 14 eyes. In these eyes, VA improved from 0.31 logMAR
170 (range: 0.18 to 0.48; 6/12) to 0.23 (range: 0.00 to 1.00; 6/10) at month 1 ($p=0.338$), and significantly
171 to 0.18 (range: 0.00 to 0.30; 6/9) at a mean final follow up of 12.9 months ($p=0.015$) (Figure 1).
172 Anatomic success occurred in 10 of 14 eyes (71%) at 1 month post-gas, and 13 of 14 eyes (93%) at
173 final follow up (Figure 2).

174 The distinction between stage 1 (impending) MH and advanced VMT relies on the investigator's
175 judgement and did not appear to be standardised in the literature. Further, impending macular hole
176 is often now grouped together with VMT. We therefore undertook a post hoc analysis combining
177 VMT and stage 1 MH. In this group, VA improved from 0.45 logMAR (range: 0.00 to 2.00; 6/17) to
178 0.43 (range: 0.00 to 2.00; 6/16) at month 1 ($p=0.382$), and then improved significantly, relative to
179 baseline, to 0.39 (range: 0.00 to 2.00; 6/15) at a mean follow up of 9.4 months ($p=0.019$). Anatomic
180 success occurred in 24 of 37 eyes (65%) at 1 month, and 31 of 37 eyes (84%) at final follow up.

181 There were 45 eyes treated with intravitreal gas for a stage 2 MH, with a mean baseline VA of 0.60
182 (range: 0.00 to 1.52; 6/24). In the 24 eyes with month 1 VA data, the mean logMAR improved to 0.54
183 (range: 0.10 to 2.00; $n = 24$; 6/21). At final follow up (mean = 17.9 months), mean VA significantly
184 improved to 0.28 logMAR (range: -0.09 to 1.00; 6/11) compared to baseline ($p<0.001$)(Figure 1).

185 Anatomic success occurred in 20 of 45 eyes (44%) at month 1, and 21 of 45 eyes (47%) at final follow
186 up (Figure 2). A PPV was undertaken in 22 eyes. In 20, the indication was failure of MH closure with
187 gas (although 17/20 had resulted in PVD), and all PPVs were successful in closing the MH. The other
188 2 PPVs were performed successfully to treat retinal detachment.

189 Two intravitreal gas procedures were performed for stage 3 MH, but neither was successful
190 anatomically either at month 1 or by a final mean follow up of 33 months.

191 The diameter of MH was only documented in one study of 20 stage 2 MH (Mori et al. 2007).
192 Successful release of vitreous traction and closure of MH at both month 1 and at an average final
193 follow up of 20 months in patients with a MH diameter $<250\mu\text{m}$ was 78% (7/9). Those with larger
194 holes ($>250\mu\text{m}$) had successful anatomical resolution in 27% of cases (3/11) at 1 month. All those
195 with failed anatomical resolution at one month underwent PPV which resulted in successful MH
196 closure.

197 Adverse events included two retinal detachments. Both occurred in myopic eyes (-5.75D and -8.50D)
198 with stage 2 MH. In two patients with VMT at baseline, intravitreal gas resulted in PVD at 1 month
199 and development of a full-thickness MH which was successfully closed with PPV. One eye with an
200 impending MH developed a full thickness MH 10 months after failed gas injection, and was
201 successfully closed with PPV. Two eyes with stage 1 MH were diagnosed with macular pseudohole at
202 month 13. There was one patient who was diagnosed with a retinal tear at 1 month following gas,
203 and underwent successful laser retinopexy. No other adverse events were reported.

204 **Discussion**

205 We undertook a review to evaluate the safety and efficacy of intravitreal gas as a treatment for
206 sVMA. We found a lack of high quality evidence. A series of uncontrolled, before/after studies found
207 that 57% of eyes had anatomic success following intravitreal gas, defined as an absence of VMT and
208 MH, without recourse to PPV. There was also a VA gain of 0.13 logMAR units (approximately 1
209 Snellen line), without the need for PPV. This modest gain in VA may not fully capture the potential
210 symptomatic benefit achieved in this patient group, given that metamorphopsia may be at least as
211 important as VA. The good presenting VA may also impose a ceiling on any VA improvement that can
212 be detected following gas injection. Studies of ocriplasmin and PPV for symptomatic VMA also show

213 modest VA gains, although the visual improvements are often better in the MH subset, compared to
214 those with isolated VMT (Jackson et al. 2013; Stalmans et al. 2012). We also found better VA gains in
215 those with a baseline diagnosis of MH compared to isolated VMT when treated with gas.

216 Our literature search found one study of 20 eyes of 17 patients with VMT that underwent an 0.2ml
217 intravitreal injection of either SF₆ or C₂F₆ (Claus et al. 2016). This was a retrospective case series
218 which reported an 85% (17/20) overall release of VMT, favourable visual acuity outcomes and no
219 major safety concerns. However, we excluded this study from our analysis because there was
220 insufficient information regarding when VMT release occurred and when post-operative visual
221 acuities were measured (Claus et al. 2016).

222 The management of symptomatic VMA does not currently have a gold standard, with options
223 including observation, intravitreal gas, ocriplasmin, and PPV. Observation of VMT may lead to
224 spontaneous separation in 17-34% of eyes, but conversely some may progress to MH, and prolonged
225 disease may result in loss of vision (Zhang et al. 2015; Almeida et al. 2015).

226 A combined analysis of two randomized controlled trials of ocriplasmin reported that 26.5% of eyes
227 responded within 1 month, with no further response after this time point. Despite using a somewhat
228 stricter definition of success (absence of both VMT and MH, not just an absence of VMT) the rate of
229 release in our review of intravitreal gas appears higher, at 48.4% by month 1 (and 57.1% at final
230 review). However, without direct comparison this conclusion needs to be interpreted with
231 considerable caution, as the difference could reflect patient selection, chance, publication bias, and
232 differences in OCT interpretation, amongst other reasons.

233 In terms of safety, there were three cases of impending MH that progressed to full-thickness MH. In
234 two cases, the gas injection resulted in PVD and full-thickness MH at one month, but the other
235 occurred 10 months after gas injection so causation is unclear. A retinal tear occurred in one case, at
236 month 1 following gas injection, which was successfully treated with laser retinopexy. Most of the

237 studies did not comment whether the patients were phakic or pseudophakic at baseline. Excluding
238 cases undergoing PPV, two eyes were noted to have progression of nuclear sclerosis but neither
239 required cataract surgery. The most clinically important AEs were two cases of retinal detachment in
240 myopic patients (2%). This suggests that myopic eyes may be best excluded from future studies of
241 intravitreal gas for symptomatic VMA. By extension it may also be reasonable to exclude other risk
242 factors for retinal detachment, such as lattice degeneration or treated retinal breaks, although the
243 risk in these patients is assumed rather than proven. The small number of eyes treated means it is
244 not possible to quantify the overall clinical impact of retinal detachment, however, any such risks
245 needs to be balanced against the risk of PPV or ocriplasmin. A recent literature review of PPV
246 undertaken for VMT found a retinal detachment rate of 4.6% (Jackson et al. 2013). The retinal
247 detachment rate in the pivotal studies of ocriplasmin was 0.4%, vs 1.6% in the placebo group
248 ($p=0.16$), although several cases of retinal detachment following ocriplasmin have now been
249 published and the true rate of RRD after ocriplasmin with longer follow up may be higher than in the
250 phase 3 trials (Haller et al. 2015; Madi et al. 2016).

251 The majority of adverse events associated with ocriplasmin have been considered mild, non-serious
252 and transient such as vitreous floaters, eye pain, photopsia and reduced VA (Kaiser et al. 2015).
253 However, concerns remain about dyschromatopsia, ERG changes and severe loss of vision, and there
254 have been isolated case reports of ellipsoid zone changes on OCT and RPE-photoreceptor adhesion
255 release potentially due to the enzymatic activity of the drug (Quezada Ruiz et al. 2015; Hager et al.
256 2015; Neffendorf et al. 2016; Abraham et al. 2016; Johnson MW et al. 2015).

257 Only one study reported MH diameter and found a higher success rate of stage 2 MH closure in
258 small diameter holes ($<250\mu\text{m}$) as opposed to those larger than $250\mu\text{m}$ (78% vs 27%). This greater
259 efficacy with smaller diameter is consistent with a sub-group analysis of the data from the pivotal
260 ocriplasmin trial (Haller et al. 2015; Jackson et al. 2016). The influence of ERM on anatomic success is
261 hard to determine as most studies excluded ERM, with only four cases included across all studies

262 (Chan et al. 1995; Day et al. 2016). Rodrigues et al reported that high reflectivity of the inner retinal
263 surface, a possible precursor of ERM, was associated with a lower rate of VMT release (Rodrigues et
264 al. 2013), which is also consistent with the sub-group analysis of the pivotal ocriplasmin trial (Haller
265 et al. 2015; Jackson et al. 2016). It has been shown that phakic patients have a higher likelihood of
266 successful sVMA release following ocriplasmin injection than pseudophakic patients (Haller et al.
267 2015; Jackson et al. 2016; Feng et al. 2017). In our analysis, only 2 of 9 articles documented whether
268 patients were phakic or pseudophakic at baseline and therefore due to missing data, we did not
269 perform a subgroup analysis to further investigate whether this trend is also seen with intravitreal
270 gas.

271 A strength of our study is that we have pooled data in a standardised method with predefined
272 outcome measures. However, there are several important weakness. Most importantly the number
273 of patients is low, and only one of the studies had a control group (and in that in turn was not
274 randomised). Accordingly, many studies may be subject to bias. Furthermore, diagnostic criteria
275 varied across studies, as did the type and volume of gas injected and the posturing regimen. Our
276 findings may underestimate VMT release in non-diabetic patients as our group contained 8% (7/91)
277 diabetics, who might be expected to have firmer VMA. In addition, some studies did not report the
278 duration of disease prior to treatment, and others had significant variability in duration (1-7
279 months). One study was conducted in the pre-OCT era, however, it provided relatively rigorous
280 assessment of VMA including B-scan ultrasonography (Chan et al. 1995). It is also not clear which gas
281 offers the best efficacy.

282 In conclusion, our synthesis of the literature suggests that there is insufficient evidence to conclude
283 on the safety and efficacy of an intravitreal expansile gas injection for the treatment of sVMA. The
284 limited results available do however appear to justify further research, most helpfully as a
285 comparative study versus other management options such as observation, ocriplasmin, or
286 vitrectomy. Diagnostic inclusion criteria can be defined using recognized photographic standards or

287 agreed classification systems (Duker et al. 2013; Steel et al. 2016), and outcome measures could be
288 expanded to include cataract progression, validated quality of life questionnaires and assessment of
289 metamorphopsia (Tanner & Williamson 2000; Ugarte et al. 2013; Khadka et al. 2013; Nomoto et al.
290 2013). An economic evaluation comparing different treatments of symptomatic VMA also appears
291 warranted, given the potential cost advantage of intravitreal gas.

292

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440 **Figure Legends**

441 **Figure 1: Visual acuity**

442 The graph shows the mean logarithm of the minimum angle of resolution visual acuity at baseline, 1
443 month after intravitreal gas injection, and at final follow up prior to vitrectomy (if carried out).
444 logMAR, logarithm of the minimum angle of resolution; MH, macular hole; VA, visual acuity; VMT,
445 vitreomacular traction.

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460 **Figure 2: Anatomic success**

461 The chart shows anatomic success, over time, of intravitreal gas injection for each subset of
462 symptomatic vitreomacular adhesion. Anatomic success was defined as an absence of vitreomacular
463 traction and macular hole, without recourse to vitrectomy. MH, macular hole; VMT; vitreomacular
464 traction.

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480 **Appendix 1: Search strategy on MEDLINE**

481 1 vitreomacular traction

482 2 vitreomacular adhesion

483 3 macular hole

484 4 or/1-3

485 5 perfluoropropane

486 6 C3F8

487 7 Octafluoropropane

488 8 Sulphur hexafluoride

489 9 Sulfur hexafluoride

490 10 SF6

491 11 Hexafluoroethane

492 12 C2F6

493 13 Gas

494 14 or/5-13

495 15 Intravitreal

496 16 4 and 14 and 15

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