Effectiveness of drug interventions to prevent delirium after surgery: a systematic review and network meta-analysis of randomized controlled trials

Supplementary file 2. Included studies

There were 41084 participants included from 158 studies. The overall incidence of postoperative delirium was 14.5% (n=5957/41084). Across the placebo arms the overall incidence of delirium was 17.1% (n=2665/15565). Among active interventions the overall incidence of delirium was 12.9% (3292/25519). Of the 337 comparisons, the majority were administered intravenously 74.7% (n=252), 16.0% (n=54) orally, and 6.8% (n=23) inhaled.

Table 1. Summary of trial characteristics

Study	**sample size**	**country**	**Intervention Arm**	**Int. events/ randomized (%)**	**Control Arm**	**Control events/ randomized (%)**	**Timing of intervention (all on day of surgery)**	**Mode of administration**	**Assessment tool**	**Postoperative ICU care (%)**
Abd Ellatif 2024[1]	120	Egypt	Arm 1: Dexmedetomidine 0.2mcg/kg/h Arm 3: Propofol 0.3-0.4mg/kg/h + Ketamine 0.125mg/kg/h	Arm1: 1/40 (2.5) Arm 3: 2/40 (5)	Equivolume saline	7/40 (17.5)	During surgery	IV	CAM-ICU	100
Aizawa 2002[2]	40	Japan	Diazepam 0.1mg/kg intramuscular + Flunitrazepam 0.04mg/kg IV infusion Pethidine 1mg/kg IV	1/20 (5)	Usual care	7/20 (35)	After surgery complete	IM/IV	DSM IV	NR
Al Tmimi 2015[3]	42	Belgium	Xenon 50-60% inhaled	2/21 (9.5)	Sevoflurane 1-1.4%	8/21 (38.1)	During surgery	INH	CAM/CAM-ICU	100*
Al Tmimi 2017[4]	50	Belgium	Xenon 30% inhaled	7/25 (28)	Propofol (Marsh model) TCI to BIS 40-60	2/25 (8)	During surgery	INH/IV	CAM	100*
Al Tmimi 2020[5]	190	Belgium	Xenon inhaled 40-60 % inhaled	41/96 (42.7)	Sevoflurane inhaled 1-1.4 %	37/94 (39.4)	During surgery	INH	3D-CAM/CAM-ICU	100*
Avidan 2017[6]	672	USA, Canada, South	Arm 1: Ketamine 1mg/kg. Arm 3: Ketamine 0.5mg/kg	Arm 1: 46/223 (19.7) Arm 3: 39/227	Equivolume saline	43/222 (19.4)	During surgery	IV	CAM/CAM-ICU	100*

		Korea, India		(17.2)						
Awada 2022[7]	63	Denmark	Methylprednisolone 10 mg/kg i.v. infused in 100 ml 0.9% saline	0/33 (0)	Dexamethasone 8mg IV	5/30 (16.7)	During surgery	IV	3DCAM	NR
Azeem 2018[8]	70	Egypt	Dexmedetomidine 1mcg/kg loading and infusion (0.4–0.7 µg/kg/h)	1/35 (2.9)	Morphine 10–50 µg/kg/h + midazolam 0.05 mg/kg to 0.2 mg/kg PRN	2/35 (5.7)	After surgery complete	IV	CAM-ICU	100*
Beloeil 2021[9]	314	France	Dexmedetomidine IV infusion 0.4-1.4mcg/kg/h	2/157 (1.3)	Remifentanil Cet IV infusion TCI 3-5ng/ml (0.1-0.25mcg/kg/min	0/157 (0)	During surgery	IV	CAM-ICU	NR
Bielza 2021[10]	152	Spain	Iron 200mg intravenous	16/74 (21.6)	Equivolume saline	17/78 (21.8)	Prior to start of surgery	IV	CAM	NR
Cao 2023[11]	1228	China	Propofol target-controlled infusion	50/614 (8.1)	Sevoflurane inhalation	74/614 (12.1)	During surgery	INH/IV	CAM/CAM-ICU	25.0
Chen 2021[12]	160	Taiwan	Dexmedetomidine 0.5mcg/kg/h	7/80 (8.8)	Equivolume saline	14/80 (17.5)	During surgery	IV	ICDSC	100
Chitnis 2022[13]	70	Canada	Dexmedetomidine IV infusion starting 0.5 mg/kg/h, titrated 0 to 1.5 mg/kg/h	8/35 (22.9)	Propofol 25 to 50 mg/kg/min	14/35 (40)	During surgery	IV	ICDSC	100*
Choovongkomol 2024[14]	200	Thailand	Dexmedetomidine 0.3-0.5mcg/kg	18/100 (18)	Equivolume saline	40/100 (40)	During surgery	IV	CAM/CAM-ICU	NR
Clemmesen 2018[15]	120	Denmark	Methylprednisolone 125mg intravenous injection	10/60 (16.7)	Equivolume saline	19/60 (31.7)	Prior to start of surgery	IV	CAM	NR
Coburn 2018[16]	256	France, Belgium, Germany, Spain, UK, Italy	Xenon 50% (MAC1)	12/124 (9.7)	sevoflurane 1.1-1.4% (MAC1)	18/132 (13.6)	During surgery	INH	CAM	NR
de Jonghe 2014[17]	395	Netherlands	Melatonin 3mg nocte	55/196 (28.1)	Placebo tablet	49/199 (24.6)	Prior to start of surgery	PO	DSMIV	Excluded ICU patients
Deiner 2017[18]	390	USA	Dexmedetomidine infusion (0.5 µg/kg/h) during surgery and up to 2 hours in the recovery room.	23/189 (12.2)	Equivolume saline	23/201 (11.4)	During surgery	IV	CAM/CAM-ICU	Excluded ICU patients

Deng 2021[19]	248	China	Methylene blue IV continuous infusion 2 mg/kg in 50ml saline	9/124 (7.3)	Equivolume saline	30/124 (24.2)	During surgery	IV	3DCAM	NR
Djaiani 2016[20]	183	Canada	Dexmedetomidine 0.4 μg/kg bolus followed by 0.2 to 0.7 μg/kg/h infusion	16/91 (17.6)	Propofol 25-50 μg/kg/min iv infusion	29/92 (31.5)	After surgery complete	IV	CAM-ICU	100*
Duan 2023[21]	296	China	Sevoflurane (1.0–1.5 MAC)	35/148 (23.6)	Propofol (2.0–3.0 mg/kg/h)	35/148 (23.6)	During surgery	INH/IV	ICDSC	100*
Duan 2024[22]	106	China	Remimazolam 0.05 mg/kg IV bolus, then 0.1-0.3 mg·kg-1·h-1 infusion	4/53 (7.5)	slow intravenous injection of propofol 0.3-0.5 mg/kg over 1 minute, followed by a maintenance dose of 0.5-3 mg·kg-1·h-1	15/53 (28.3)	During surgery	IV	CAM	NR
Farrer 2023[23]	199	USA	TIVA propofol plus fentanyl	13/100 (13)	Isoflurane (plus fentanyl) BIS 40-60	14/99 (14.1)	During surgery	INH/IV	CAM	NR
Fazel 2022[24]	80	Iran	Melatonin 5mg PO	8/40 (20)	Placebo tablet	16/40 (40)	Prior to start of surgery	PO	AMT	NR
Ford 2020[25]	207	Australia	Melatonin 3mg capsules	21/100 (21)	Placebo capsule	21/105 (20)	Prior to start of surgery	PO	CAM	NR
Gajniak 2023[26]	70	Poland	lidocaine bolus of 1.5 mg/kg, followed by continuous infusion of 1–3 mg/kg/h intraoperatively, and the dose of 1–3 mg/kg/h maintained for 24–48 h after surgery	1/33 (3)	Equivolume saline	6/37 (16.2)	During surgery	IV	CAM	2.9
Gamberini 2009[27]	113	Switzerland	Rivastigmine 1.5 mg oral TDS	18/57 (31.6)	Placebo tablet	17/56 (30.4)	Prior to start of surgery	PO	CAM	100*
Gao 2020[28]	60	China	Dexmedetomidine 1mcg/kg bolus, 0.3-0.5mcg/kg/h infusion	3/30 (10)	Equivolume saline	9/30 (30)	During surgery	IV	APA	100*
Gao 2021[29]	40	China	Dexmedetomidine loading dose0.6μg/kg , continuous infusion 0.2μg/kg/h	3/20 (15)	Equivolume saline	10/20 (50)	During surgery	IV	DSM IV	100*
Ghazaly 2023[30]	60	Egypt	Arm 1: Dexmedetomidine 1mcg/kg, Arm 3: Ketamine 1mg/kg	Arm1: 1/20 (5) Arm 3: 2/20 (10)	Equivolume saline	15/20 (75)	During surgery	IV	DOS	Excluded ICU patients
Greenberg 2018[31]	140	USA	Acetaminophen 1000 mg IV	1/70 (1.4)	Equivolume saline	0/70 (0)	After surgery	IV	CAM-ICU	NR

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Guo 2015[32]	156	China	Dexmedetomidine 0.2mcg/kg/h	6/78 (7.7)	Equivolume saline	21/78 (26.9)	After surgery complete	IV	CAM-ICU	100
Gupta 2019[33]	100	India	Ramelteon 8mg tablet oral	2/50 (4)	Placebo tablet	6/50 (12)	Prior to start of surgery	PO	CAM	NR
Haller 2021[34]	140	Hong Kong, Switzerland	N2O 70%, 30% O2	0/72 (0)	Air 70%, 30% O2	1/68 (1.5)	During surgery	INH	DSM4	12.1
Harmon 2004[35]	36	Ireland	Aprotinin 2 × 10^6 KIU (loading dose), 2 × 10^6 KIU (added to circuit prime) and a continuous infusion of 5 × 10^5 KIU·hr–1	1/18 (5.6)	Placebo injection	3/18 (16.7)	During surgery	IV	DSM-III-R criteria,	100*
He 2021[36]	60	China	Dexmedetomidine 0.1 μg/kg/hour IV infusion	2/30 (6.7)	Equivolume saline	3/30 (10)	After surgery complete	IV	CAM-ICU	100
He 2022[37]	80	China	Dexmedetomidine 1mcg/kg bolus, 0.5mcg/kg/h infusion	3/40 (7.5)	Equivolume saline	10/40 (25)	During surgery	IV	CAM	Excluded ICU patients
He 2023[38]	60	China	Dexmedetomidine 0.5mcg/kg intravenous bolus, 0.2mcg/kg/h infusion	3/30 (10)	Equivolume saline	13/30 (43.3)	During surgery	IV	CAM	NR
He 2024[39]	120	China	Arm 1: Alprazolam 0.4mg PO, Arm 3: Dexmedetomidine 1.5mcg/kg IN	Arm1: 15/40 (37.5) Arm 3: 5/40 (12.5)	Equivolume saline	13/40 (32.5)	Prior to start of surgery	IV	CAM	NR
Hollinger 2021[40]	182	Switzerland	Arm 1: Haloperidol 5mcg/kg IV, Arm 3: Ketamine 1mg/kg IV, Arm 4: Haloperidol 5mcg/kg + Ketamine 1mg/kg IV	Arm 1: 7/45 (15.6) Arm 3: 10/47 (21.3) Arm 4: 3/46 (6.5)	Placebo injection	6/44 (13.6)	During surgery	IV	DOS/NuDESC / ICDSC	Excluded ICU patients
Hong 2021[41]	712	China	Dexmedetomidine 2.5mcg IV bolus PCA lockout 8 min, background infusion of 1.25mcg/h	17/356 (4.8)	Equivolume saline	26/356 (7.3)	After surgery complete	IV	CAM/CAM-ICU	2.0
Hongyu 2019[42]	90	China	Arm 1: Penehyclidine 10mcg/kg IM, Arm 3: Atropine 10mcg/kg	Arm 1: 16/30 (53.3) Arm 3: 7/30 (23.3)	Equivolume saline	5/30 (16.7)	During surgery	IV	CAM	NR
Hu 2021[43]	177	China	Dexmedetomidine 0.4mcg/kg bolus over 15 minutes before induction, 0.1mcg/kg/h infusion	15/90 (16.7)	Equivolume saline	32/87 (36.8)	During surgery	IV	CAM	Excluded ICU

			until 1h before end of surgery							patients
Hu 2022[44]	60	China	Arm 1: Dexmedetomidine 0.04 mg/mL intravenous bolus, infusion 0.4 µg/kg/h, Arm 3: Dexmedetomidine intravenous bolus 0.04 mg/mL, infusion 0.4 µg/kg/h+40mg atorvastatin daily	Arm 1: 1/20 (5) Arm 3: 1/20 (5)	Equivolume saline	3/20 (15)	During surgery	IV	CAM criteria	NR
Huang 2021[45]	90	China	Insulin 20 units intranasal	5/45 (11.1)	Equivolume saline	19/45 (42.2)	Prior to start of surgery	IV	CAM-ICU	NR
Huang 2023[46]	160	China	Dexamethasone 10mg intravenous bolus	9/80 (11.2)	Equivolume saline	21/80 (26.2)	Prior to start of surgery	IV	CAM-ICU	100
Huang 2023[47]	90	China	Arm 1: Insulin 20 units intranasal. Arm 3: Insulin 30 units intranasal	Arm1 : 9/30 (10) Arm 3: 1/30 (3)	Equivolume saline	19/30 (63.3)	During surgery	IV	Nu-DESC	NR
Hudetz 2009[48]	58	USA	Ketamine 0.5 mg/kg iv bolus	1/29 (3.4)	Equivolume saline	9/29 (31)	During surgery	IV	ICDSC	100*
Huet 2024[49]	333	France	Dexmedetomidine intravenous 0.1-1.4mcg/kg/h Infusion	20/166 (12)	Equivolume saline	20/167 (12)	After surgery complete	IV	CAM-ICU	100*
Ishii 2016[50]	59	Japan	Propofol 1.5-3 µg/mL Cet TCI	2/29 (6.9)	Sevoflurane with 1 to 1.5 minimum alveolar concentration	8/30 (26.7)	During surgery	INH/IV	CAM-ICU	100
Jaiswal 2019[52]	117	USA	Ramelteon 8mg tablet oral	19/59 (32.2)	Placebo tablet	22/58 (37.9)	Prior to start of surgery	PO	CAM-ICU	100*
Javaherforoos hzadeh 2021[53]	60	Iran	Melatonin 3mg tablet	4/30 (13.3)	Placebo tablet	11/30 (36.7)	Prior to start of surgery	PO	CAM-ICU	100*
Javaherforoos hzadeh 2023[54]	80	Iran	Melatonin 3mg tablet	6/40 (15)	Placebo tablet	12/40 (30)	Prior to start of surgery	PO	CAM/CAM-ICU	100*
Jeon 2023[55]	132	South Korea	Remimazolam 6mg/kg/h induction, 1-2mg/kg/h maintenance BIS 50	0/66 (0)	Propofol (Schneider 4mcg/ml Cet) induction, 2.5-4mcg/ml maintenance BIS 50	0/66 (0)	During surgery	IV	DSM V	0.8
Jiang 2023[51]	698	China	Sevoflurane or desflurane minimum Et conc 0.5 - 2 MAC inhaled	76/349 (21.8)	Propofol 3-8mg/kg/h	63/349 (18.1)	During surgery	INH/IV	CAM-ICU	100*
Kalisvaart	430	Netherla	0.5mg Haloperidol PO	32/212 (15.1)	placebo_tablet	36/218 (16.5)	After	PO	CAM/D	NR

2005[56]		nds					surgery complete		SM IV	
Kanamori 2023[57]	64	Japan	Magnesium 30mg/kg iv bolus (1h), 10mg/kg/h infusion (max 3h)	2/31 (6.5)	Equivolume saline	2/33 (6.1)	During surgery	IV	CAM-ICU	100
Kaneko 1999[58]	80	Japan	Haloperidol 5mg IV	4/40 (10)	Equivolume saline	13/40 (32.5)	After surgery complete	IV	DSM III-R	NR
Khan 2018[59]	135	USA	Haloperidol 0.5mg iv bolus	15/68 (22.1)	Equivolume saline	19/67 (28.4)	After surgery complete	IV	CAM/CAM-ICU	100
Kim 2019[60]	143	South Korea	Dexmedetomidine 0.5mcg/kg/h, BIS 45 +/-5	15/73 (20.5)	Equivolume saline	15/70 (21.4)	During surgery	IV	CAM/CAM-ICU	100
Kinouchi 2023[61]	108	Japan	ramelteon 8mg tablet oral	7/55 (12.7)	Placebo tablet	4/53 (7.5)	Prior to start of surgery	PO	CAM-ICU	NR
Kluger 2021[62]	79	New Zealand	Dexamethasone 20 mg intravenous injection	6/40 (15)	Equivolume saline	9/39 (23.1)	Prior to start of surgery	IV	4AT	NR
Lai 2023[63]	90	China	Arm 1: Dexmedetomidine 1 mcg/kg 10 minute IV bolus, continuous infusion 0.5 mcg/kg/h. Arm 3: Lidocaine 1mg/kg bolus, 1mg/kg lidocaine infusion	Arm 1: 5/30 (16.7) Arm 3: 9/30 (30)	Equivolume saline	4/30 (13.3)	During surgery	IV	3DCAM	NR
Larsen 2010[64]	495	USA	Olanzapine 5mg PO	28/243 (11.5)	Placebo tablet	82/252 (32.5)	Prior to start of surgery	PO	CAM/DSM-III-R	NR
Lee 2018[65]	345	South Korea	Arm 1: Dexmedetomidine 1 µg/kg bolus followed by 0.2 to 0.7 µg/kg/h infusion. Arm 3: Dexmedetomidine 1 µg/kg bolus	Arm 1: 9/111 (8.1) Arm 3: 21/118 (17.8)	Equivolume saline	27/116 (23.3)	During surgery	IV	CAM	17.7
Lee 2020[66]	215	South Korea	Dexmedetomidine 0.1mcg/kg/h infusion	9/107 (8.4)	Equivolume saline	6/108 (5.6)	During surgery	IV	CAM-ICU	100
Leung 2006[67]	210	USA	N2O with O2	44/105 (41.9)	O2 (with or without air)	46/105 (43.8)	During surgery	INH	CAM	NR
Leung 2006[68]	21	USA	Gabapentin 900mg PO	0/9 (0)	Placebo tablet	5/12 (41.7)	Prior to start of surgery	PO	CAM	NR

Leung 2017[69]	697	USA	Gabapentin 900mg PO	84/350 (24)	Placebo tablet	75/347 (21.6)	Prior to start of surgery	PO	CAM	NR
Li 2013[70]	80	China	Parecoxib sodium 40 mg intravenously (reduce to 20mg if <50kg)	9/40 (22.5)	Morphine 2/4mg then saline	18/40 (45)	After surgery complete	IV	DSM IV	NR
Li 2017[71]	285	China	Dexmedetomidine iv bolus 0.6 μg/kg for 10 minutes, 0.4 μg/k/h intraop, 0.1mcg.kg.h postop until extubation	7/142 (4.9)	Equivolume saline	11/143 (7.7)	During surgery	IV	CAM/CAM-ICU	100*
Li 2020[72]	619	China	Dexmedetomidine (0·6 μg/kg) bolus, infusion 0·125 ml per kg per h (0·5 μg per kg per h)	17/309 (5.5)	Equivolume saline	32/310 (10.3)	During surgery	IV	CAM/CAM-ICU	14.7
Li 2023[73]	106	China	1% Lidocaine 1 mg/kg (0.15 mL/kg) bolus, 0.15 mL/(kg·h) until the end of surgery	7/53 (13.2)	Equivolume saline	18/53 (34)	During surgery	IV	CAM	NR
Li 2023[74]	260	China	Dexmedetomidine 0.6 mg/k 10 minute IV bolus, continuous infusion then 0.4 mg/kg/h	28/130 (21.5)	Equivolume saline	60/130 (46.2)	During surgery	IV	CAM-ICU	16.2
Likhvantsev 2021[75]	175	Russia	Dexmedetomidine 0.7mcg/kg/h intraop, titrated 0.4-1.4mcg/kg/h in ICU	6/87 (6.9)	Equivolume saline	16/88 (18.2)	During surgery	IV	CAM-ICU	100*
Lin 2022[76]	170	China	Hydrogen FiH2 0.667	10/85 (11.8)	Oxygen FiO2 0.33	17/85 (20)	Prior to start of surgery	INH/IV	CAM	NR
Liu 2016[77]	61	China	Dexmedetomidine (0.2-1.5 μg/kg/h) iv infusion	0/33 (0)	Propofol (5-50 μg/kg/min)	2/34 (5.8)	During surgery	IV	CAM	1.5
Liu 2016[78]	197	China	Dexmedetomidine 0.2–0.4 mcg/kg/h	15/99 (15.2)	Equivolume saline	43/98 (43.9)	After surgery complete	IV	CAM-ICU	100*
Liu 2021[79]	120	China	Dexmedetomidine 0.5 mcg/kg 10 minute IV bolus, continuous infusion then 0.4 mcg/kg/h	5/60 (8.3)	Equivolume saline	8/60 (13.3)	During surgery	IV	3DCAM	Excluded ICU patients
Liu 2023[80]	304	China	Dexmedetomidine 0.5 μg.kg−1 bolus, maintenance infusion 0.2 μg.kg−1.hr−1	32/152 (21.1)	Equivolume saline	36/152 (23.7)	During surgery	IV	CAM	NR
Liu 2024[81]	105	China	Ciprofol 0.3-0.4mg/kg induction, 1-2.4mg/kg/h maintenance, BIS 40-60	3/53 (5.7)	Propofol 1.0–1.5 mg/kg bolus, 4-12mg/kg/h infusion maintenance, BIS 40-	7/52 (13.5)	During surgery	IV	CAM	NR

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Long 2024[82]	78	China	Dexmedetomidine 0.5 μg/kg/h intravenous infusion	3/39 (7.7)	Equivolume saline	7/39 (17.9)	During surgery	IV	3DCAM /CAM-ICU	3.8
Lu 2021[83]	808	China	Dexmedetomidine bolus 0.5 μg/kg IV, maintenance 0.2 μg/kg per hour	41/404 (10.1)	Equivolume saline	43/404 (10.6)	During surgery	IV	CAM	NR
Lu 2023[84]	94	China	Dexmedetomidine 0.7 μg/kg IV bolus, 0.2-0.5 μg/kg/h infusion	9/47 (19.1)	Esketamine 0.5 mg/kg IV	2/47 (4.3)	During surgery	IV	CAM	NR
Lurati Buse 2012[85]	385	Switzerland	propofol	29/201 (14.4)	Sevoflurane inhaled	21/184 (11.4)	During surgery	INH/IV	CAM	NR
Lv 2022[86]	327	China	Dexmedetomidine 0.1 μg/kg/h	21/163 (12.9)	Equivolume saline	46/164 (28)	After surgery complete	IV	CAM	100
Ma 2013[87]	120	China	Arm 1: Dexmedetomidine 1mcg/kg, infusion 0.5mcg/kg/h. Arm 3: Ketamine 0.5mg/kg, Arm 4: Dexmedetomidine 1mcg/kg, infusion 0.5mcg/kg/h + Ketamine 0.5mg/kg	Arm 1: 2/30 (6.7) Arm 3: 8/30 (26.7) Arm 4: 0/30 (0)	Equivolume saline	3/30 (10)	During surgery	IV	CAM	NR
Ma 2023[88]	62	China	Esketamine 0.25 mg/kg induction; 0.125 mg/kg/h maintenance	3/31 (9.7)	Equivolume saline	4/31 (12.9)	During surgery	IV	CAM-ICU	Excluded ICU patients
Mahrose 2021[89]	110	Egypt	Melatonin tablet 5 mg	6/55 (10.9)	Usual care	15/55 (27.3)	Prior to start of surgery	PO	CAM/CAM-ICU	100*
Maldonado 2009[90]	118	USA	Arm 1: Dexmedetomidine 0.4 μg/kg bolus followed by 0.2 to 0.7 μg/kg/h infusion Arm 3: Midazolam 0.5-2mg/h	Arm 1: 1/40 (5) Arm 3: 15/40 (37.5)	Propofol 25-50mcg/kg/min	15/38 (39.5)	During surgery	IV	DSM IV-TR	100*
Marcantonio 2011[91]	16	USA	Donepezil 5 mg PO	3/7 (42.9)	Placebo tablet	3/9 (33.3)	Prior to start of surgery	PO	CAM	NR
Mardani 2013[92]	93	Iran	Dexamethasone 8 mg IV	4/43 (9.3)	Equivolume saline	13/50 (26)	During surgery	IV	DSM-IV	100*
Massoudi 2023[93]	100	Iran	Rivastigmine 1.5 mg orally	4/50 (8)	Placebo tablet	12/50 (24)	Prior to start of surgery	PO	CAM	100
Massoumi 2019[94]	90	Iran	Dexmedetomidine 1 μg/kg bolus, infusion of 0.2-0.7 μg/kg/h	4/45 (8.9)	Equivolume saline	9/45 (20)	During	IV	CAM-	100*

							surgery		ICU	
Mei 2018[95]	336	China	Dexmedetomidine 0.8-1mcg/kg bolus over 15-20min, infusion 0.1-0.5mcg/kg/h	11/167 (6.6)	Propofol TCI 0.8-1mcg/ml Cet	24/169 (14.2)	During surgery	IV	CAM	NR
Mei 2020[96]	240	China	Propofol TCI	35/122 (28.7)	Sevoflurane 1%−4%	24/118 (20.3)	During surgery	INH/IV	CAM	NR
Mei 2020[97]	415	China	Dexmedetomidine 0.8-1mcg/kg bolus over 15-20min, infusion 0.1-0.5mcg/kg/h	26/207 (12.6)	Propofol TCI 0.8-1mcg/ml Cet	43/208 (20.7)	During surgery	IV	CAM	NR
Mohamed 2022[98]	80	Egypt	Melatonin 5mg PO	10/40 (25)	Paracetamol 500mg	21/40 (52.5)	Prior to start of surgery	PO	AMT	NR
Mohammadi 2016[99]	45	Iran	Cyproheptadine 4mg TDS orally	3/23 (13)	Placebo tablet	7/22 (31.8)	After surgery complete	PO	CAM-ICU	100
Momeni 2021[100]	417	Belgium	dexmedetomidine 0.4mg/kg/h	31/208 (14.9)	Equivolume saline	33/209 (15.8)	During surgery	IV	CAM-ICU/CAM	100*
Moslemi 2020[101]	96	Iran	Thiamine 200 mg IV	4/48 (8.3)	Equivolume saline	12/48 (25)	After surgery complete	IV	CAM-ICU	100
Mu 2017[102]	620	China	40mg parecoxib iv bolus	19/310 (6.1)	Equivolume saline	34/310 (11)	After surgery complete	IV	CAM/CAM-ICU	6.3
Nishikawa 2004[103]	50	Japan	Propofol 4mg/ml TCI	4/25 (16)	Sevoflurane inhaled	0/25 (0)	During surgery	INH/IV	DRS	NR
Niu 2023[104]	149	China	Arm 1: Dexmedetomidine 0.6mg/kg IV bolus. Arm 3: Dexmedetomidine 0.6mcg/kg endotracheal	Arm 1: 3/49 (6.1) Arm 3: 5/50 (10)	Dexmedetomidine 1mcg/kg intranasal	14/50 (28)	During surgery	INH/IV/IN	3DCAM	Excluded ICU patients
Oh 2021[105]	80	USA	8 mg Ramelteon orally	3/41 (7.3)	Placebo tablet	2/39 (5.1)	Prior to start of surgery	PO	CAM/DSM V	0.0
Papadopoulos 2014[106]	106	Greece	Ondansetron 8mg intravenous bolus	18/51 (35.3)	Placebo injection	29/55 (52.7)	After surgery complete	IV	CAM	NR
Park 2014[107]	142	South Korea	Dexmedetomidine iv bolus (0.5 μg/kg) then infusion 0.2 -0.8 μg/kg/hr	6/67 (9)	Remifentanil 1-2.5ng/hr	17/75 (22.7)	After surgery complete	IV	CAM-ICU	100*

Prakanrattana 2007[108]	126	Thailand	Risperidone 1mg (oral dissolving) tablet	7/63 (11.1)	Dissolving sublingual placebo strip	20/63 (31.7)	After surgery complete	PO	CAM-ICU	100*
Preveden 2023[109]	120	Serbia	Dexmedetomidine infusion in doses 0.2-0.7 mcg/kg/h	7/60 (11.7)	Propofol infusion in doses 1-2 mg/kg/h.	15/60 (25)	After surgery complete	IV	CAM-ICU	100*
Qi 2023[110]	62	China	Esketamine 0.3mg/kg intravenous bolus, 0.25mg/kg/h infusion	2/31 (6.5)	Equivolume saline	7/31 (22.6)	During surgery	IV	CAM	NR
Qu 2023[111]	394	USA	Dexmedetomidine (1 μg/kg over 40 min), maximal dose of 80 μg	5/188 (2.7)	Equivolume saline	16/206 (7.8)	After surgery complete	IV	CAM	100*
Robinson 2014[112]	301	USA	L-tryptophan 1 gram enterally	61/152 (40.1)	Placebo tablet	55/149 (36.9)	After surgery complete	PO	CAM-ICU	100*
Royse 2011[113]	182	Australia	Propofol 1.5-3 mcg.ml TCI induction Marsh, BIS40-60 maintenance	7/91 (7.7)	Sevoflurane induction, Desflurane maintenance BIS40-60	12/91 (13.2)	During surgery	INH/IV	CAM	100*
Sakic 2023[114]	60	Croatia	Dexamethasone 8mg intrathecal	1/30 (3.3)	Equivolume saline	5/30 (16.7)	During surgery	IT	CAM	NR
Sampson 2007[115]	36	UK	Donepezil 5 mg PO	2/21 (9.5)	Placebo tablet	5/15 (33.3)	After surgery complete	PO	Delirium Symptom Interview	NR
Sauer 2014[116]	737	Netherlands	Dexamethasone 1 mg/kg (100 mg maximum) single intravenous injection	52/367 (14.2)	Equivolume saline	55/370 (14.9)	During surgery	IV	CAM/CAM-ICU	100*
Shehabi 2009[117]	306	Australia	Dexmedetomidine iv infusion 0.1–0.7 mcg/k/h	13/154 (8.4)	Morphine iv infusion 10-70mcg/kg/h	22/152 (14.5)	After surgery complete	IV	CAM-ICU	100*
Shen 2022[118]	120	China	Flurbiprofen 100mg iv infusion	7/60 (11.7)	Equivolume saline	15/60 (25)	During surgery	IV	CAM/CAM-ICU	NR
Shin 2023[119]	748	South Korea	Dexmedetomidine 1mcg/kg loading and infusion (0.1–0.5 μg/kg/h)	11/374 (2.9)	Propofol TCI 1-2mcg/ml Cet	24/374 (6.4)	During surgery	IV	CAM	0.1
Shokri 2020[120]	286	Egypt	Dexmedetomidine 0.7–1.2 μg/kg/h (max 1.4). 24h or ICU	12/144 (8.3)	Clonidine 0.5mcg/kg bolus then IV infusion	23/142 (16.2)	After surgery	IV	CAM-ICU	100*

			discharge		of 1–2 μg/kg/h		complete			
Siripoonyothai 2021[121]	75	Thailand	Ketamine 1-2 mg/kg/hr continuous infusion during CPB	10/37 (27)	Propofol 25-100 mcg/kg/min continuous infusion during CPB	18/38 (47.4)	During surgery	IV	CAM	100*
Soh 2020[122]	108	South Korea	Dexmedetomidine 0.4 mg/kg/h	2/54 (3.7)	Equivolume saline	7/54 (13)	During surgery	IV	DSM V	100*
Spies 2021[123]	277	Germany	Physostigmine intravenous bolus 0.02 mg/kg, then 0.01 mg/kg/h	26/136 (19.1)	Placebo injection	20/141 (14.2)	During surgery	IV	DSM IV-TR	100
Stoppe 2023[124]	1394	Germany, Canada	Selenium intravenous high-dose supplementation 2000 μg/L immediately postoperatively, 1000 μg/L each day in intensive care for a maximum of 10 days	112/697 (16.1)	Placebo injection	127/697 (18.2)	During surgery	IV	CAM-ICU	100*
Su 2016[125]	700	China	Dexmedetomidine infusion (0.1 μg/kg/h)	32/350 (9.1)	Equivolume saline	79/350 (22.6)	After surgery complete	IV	CAM-ICU	100
Subramaniam 2019[126]	120	USA	Arm 1: Dexmedetomidine 0.5 -1mcg/kg IV during chest closure, followed by a maintenance infusion of 0.1 -1.4 mcg/kg/hour + Acetaminophen (dose not specified). Arm 3: Dexmedetomidine 0.5 -1mcg/kg IV during chest closure, followed by a maintenance infusion of 0.1 -1.4 mcg/kg/hour. Arm 4: Propofol 20-100mcg/kg/min + acetaminophen (dose not specified)	Arm 1: 2/29 (6.9) Arm 3: 8/30 (26.7) Arm 4: 4/31 (12.9)	Propofol 20-100mcg/kg/min	9/30 (30)	After surgery complete	IV	CAM/CAM-ICU	100*
Sultan 2010[127]	203	Egypt	Arm 1: Melatonin 5mg tablet. Arm 3: Midazolam 7.5mg tablet. Arm 4: Clonidine 100mcg tablet	Arm 1: 5/53 (9.4) Arm 3: 22/50 (44.0) Arm 4: 19/51 (37.2)	Usual care	16/49 (32.7)	Prior to start of surgery	PO	AMT	Excluded ICU patients
Takazawa 2023[128]	202	Japan	Minocycline 100mg PO	5/100 (5)	placebo_tablet	3/102 (2.9)	Prior to start of surgery	PO	CAM-ICU	NR
Tanaka 2017[129]	90	USA	Desflurane inhaled, PSI target 30-50	0/45 (0)	Propofol infusion, PSI target 30-50	1/45 (2.2)	During surgery	INH/IV	CAM	NR
Tang 2022[130]	120	China	Arm 1: Dexmedetomidine 0.3 μg/kg/h. Arm 3: Dexmedetomidine	Arm 1: 2/40 (5) Arm 3: 3/40 (7.5)	Equivolume saline	9/40 (22.5)	During surgery	IV	CAM	NR

			0.6 μg/kg/h							
Turan 2020[131]	794	USA	Dexmedetomidine 0.1mcg/kg/h induction, 0.2 on CPB, 0.4 in ICU. Stopped by 24hours.	67/398 (16.8)	Equivolume saline	46/396 (11.6)	During surgery	IV	CAM-ICU	100*
van Norden 2021[132]	60	Germany	Dexmedetomidine 0.7 mcg.kg-1.h-1	5/28 (17.9)	Equivolume saline	14/32 (43.8)	During surgery	IV	CAM	NR
Vlisides 2021[133]	65	USA	Caffeine 200mg IV infusion over 1 hour	7/34 (20.6)	Equivolume 5% dextrose	14/31 (45.2)	After surgery complete	IV	CAM	NR
Wang 2012[134]	457	China	Haloperidol 0.5 mg intravenous bolus, then infusion at a rate of 0.1 mg/h for 12 hrs	35/229 (15.3)	Equivolume saline	53/228 (23.2)	After surgery complete	IV	CAM-ICU	100
Wang 2021[135]	70	China	Parecoxib sodium 40 mg intravenously	2/35 (5.7)	Equivolume saline	8/35 (22.9)	During surgery	IV	DRS	NR
Wang 2023[136]	652	China	Dexmedetomidine intravenous bolus 0.6 μg kg−1 then 0.4 μg.kg−1.h−1	47/326 (14.4)	Equivolume saline	51/326 (15.6)	Prior to start of surgery	IV	CAM	NR
Wang 2023[137]	80	China	40mg parecoxib iv bolus	4/40 (10)	Equivolume saline	11/40 (27.5)	During surgery	IV	CAM-ICU	100*
Wang 2024[138]	120	China	Esketamine 0.5mg/kg intravenous bolus	18/63 (28.6)	Equivolume saline	19/57 (33.3)	During surgery	IV	CAM	Excluded ICU patients
Whitlock 2015[139]	7507	Canada, China, India, USA, Colombia, Australia, Italy, Iran, Czech Republic, Greece, Spain, Brazil, Austria, Belgium, Hong	Methylprednisolone 250mg iv bolus	295/3755 (7.9)	Placebo injection	289/3752 (7.7)	During surgery	IV	CAM-ICU	100*

		Kong, Argentina, Chile, Ireland								
Wittwer 2023[140]	52	USA	Ketamine 1-2mg/kg iv bolus	0/26 (0)	Propofol 0.5-1mg/kg	1/26 (3.8)	During surgery	IV	CAM	100*
Wu 2023[141]	115	China	Dexmedetomidine intranasal 2mcg/kg	3/58 (5.2)	Equivolume saline	7/57 (12.3)	After surgery complete	IN/IV	3DCAM	Excluded ICU patients
Xiang 2022[142]	171	China	Methylprednisolone 2 mg/kg IV bolus	9/85 (10.6)	Equivolume saline	20/86 (23.3)	During surgery	IV	CAM-ICU	NR
Xie 2021[143]	160	China	Edavarone 30mg over 30 min IV infusion	12/80 (15)	Equivolume saline	25/80 (31.2)	During surgery	IV	CAM	1.9
Xie 2023[144]	240	China	PCIA Dexmedetomidine 3mcg/kg & sufentanil 3mcg/kg, total amount 150 ml, 2 ml bolus dose with a lock-out of 10 min and background infusion rate 2 ml/h.	4/120 (3.3)	Equivolume saline	12/120 (10)	After surgery complete	IV	CAM-ICU	71.3
Xin 2021[145]	60	China	Dexmedetomidine 0.5 μg/kg dexmedetomidine over 10 minutes before anesthesia induction, continuous infusion of 0.4 μg/kg/h until 30 minutes before the end of surgery	3/30 (10)	Equivolume saline	10/30 (33.3)	During surgery	IV	3DCAM	NR
Xing 2021[146]	110	China	Dexmedetomidine 0.5 mg/kg IV bolus	2/55 (3.6)	Equivolume saline	8/55 (14.5)	During surgery	IV	Chinese Expert Consensus	NR
Xu 2021[147]	821	China	40 mg Rosuvastatin PO	23/410 (5.6)	Placebo tablet	42/411 (10.2)	Prior to start of surgery	PO	CAM/CAM-ICU	100
Yang 2015[148]	80	China	Dexmedetomidine(4μg/mL) : 0.5μg/kg/hr infusion for 1 hour before operation is completed and 0.2-0.7μg/kg/hr infusion continuously until 6:00am the next day	2/40 (5)	Equivolume saline	5/40 (12.5)	During surgery	IV	CAM-ICU	100
Yang 2023[149]	111	China	Quetiapine 12.5mg PO	8/57 (14)	Placebo tablet	12/54 (22.2)	During surgery	IV	CAM	1.6

Yang 2023[150]	315	China	Remimazolam (0.2–0.3 mg/kg bolus, variable infusion maintenance)	23/155 (14.8)	Propofol (1.0–1.5 mg/kg bolus, variable infusion maintenance)	19/160 (11.9)	Prior to start of surgery	PO	CAM	NR
Yoo 2024[151]	128	South Korea	Dexmedetomidine 1 mcg/kg 10 minute IV bolus, continuous infusion then 0.2 mcg/kg/h	4/64 (6.2)	Equivolume saline	10/64 (15.6)	During surgery	IV	CAM-ICU	Excluded ICU patients
Youn 2017[152]	62	South Korea	Rivastigmine 4.6mg patch	5/31 (16.1)	Usual care	14/31 (45.2)	Prior to start of surgery	Patch	CAM	NR
Yuefeng 2021[153]	60	China	Dexmedetomidine 0.6mcg/kg bolus over 15 minutes before induction, 0.2mcg/kg/h infusion until 30 min before end of surgery	1/30 (3.3)	NR	3/30 (10)	During surgery	IV	CAM	NR
Zhang 2020[154]	232	China	Dexmedetomidine intravenous 0.5 mcg/kg/h bolus, 0.3mcg/kg/h infusion	20/116 (17.2)	Equivolume saline	36/116 (31)	During surgery	IV	CAM	NR
Zhang 2023[155]	117	China	Dexmedetomidine 0.2mcg/kg/h	2/58 (3.4)	Equivolume saline	0/59 (0)	After surgery complete	IV	CAM-ICU	1.7
Zhao 2020[156]	416	China	Arm 1: Dexmedetomidine 0.02 mcg/kg/h, Arm 3: Dexmedetomidine 0.04 mcg/kg/h, Arm 4: Dexmedetomidine 0.08 mcg/kg/h	Arm 1: 15/108 (13.8) Arm 3: 5/105 (4.7) Arm 4: 5/102 (4.9)	Equivolume saline	19/101 (18.8)	During surgery	IV	CAM	NR
Zhou 2022[157]	125	China	Propofol (4.0–8.0 mg/kg−1/h−1) IV infusion	14/63 (22.2)	Sevoflurane 1-1.5%	13/62 (21)	During surgery	INH/IV	CAM	NR
Zhu 2023[158]	226	China	Dexmedetomidine 0.3 μg/kg IV bolus, followed by continuous administration of 0.2–0.7 μg/kg per hour. (MOAA/S) score. The target sedation level was <2 points (lighter sedation group) or >3 points (heavier sedation group)	26/113 (23)	Propofol 0.5–3.0 mg/kg per hour	13/113 (11.5)	During surgery	IV	CAM	NR

IV, intravenous; PO, per oral; INH, inhaled; IT, intrathecal; IN, intranasal; ICU, intensive care unit; NR, not reported; *including patients admitted to ICU for extubation

At the request of a reviewer the proportion of participants admitted to intensive care postoperatively was also extracted. There were 58% (n=92) studies reporting the proportion admitted to intensive care after surgery, 42% did not report this information, 67% (n=62) studies reporting ICU admission did not differentiate admission to ‘ICU’ for extubation or monitoring only from admission to ICU for ongoing critical/severe illness. In the remaining 11% (n=17) studies which reported ICU admission rates the median (IQR) proportion was 2.9 (1.5 to 14.7)%.

Table 2. Summary of timing of first administration of intervention

Number of trials	Time of first administration	Percentage of all trials
30	On the day of surgery, prior to start of surgery	19.0
95	On the day of surgery, during surgery	60.1
30	On the day of surgery, after surgery complete	20.1

Table 3. Summary of validated delirium assessment tools used

Assessment tool	Number of trials using the tool*
CAM	79
CAM-ICU	62
DSM	15
3DCAM	9
ICDSC	5
AMT	3
DOS	2
DRS	2
NuDESC	2
4AT	1
APA	1
Delirium Symptom Interview	1
Other	1

The assessment tools reported were for the delirium outcome. Other tools e.g. CAM-S, MDAS were used adjunctively in trials where delirium severity was assess as a secondary outcome (see Supplementary file 1).
*Note the total will exceed 158 trials for instances where trials used both CAM and CAM-ICU.

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