Supplementary data 1 - Trial characteristics

Reference	Group (n)	Surgery	Opioid regimen		Anaesthetic maintenance	PONV prevention	Postoperative analgesia	Outcomes
			Control	Opioid				
Bakan et Al. 2015	OFA (43) OBA (42)	Laparoscopic cholecystectomy	Dexmedetomidine I : 0.6 ug/kg in 10 min M : 0.3 ug/kg/h Lidocaine I : 1.5 mg/kg M : 2 mg/kg/h	Fentanyl I : 2 ug/kg M : 15 ug/kg/h	Propofol I : 1.5mg/kg M : 10mg/kg/h	8mg i.v Dexamethasone	Fentanyl i.v PCA	Opioid consumption, postoperative pain, side effect
Beloeil et Al. 2021	OFA (158) OBA (158)	Major and intermediate non cardiac surgery	Dexmedetomidine I/M : 0.4 to 1.4 µg/kg/h	Remifentanil I/M : TCI 3 to 5 ng/ml i.v Morphine bolus of 0.05 mg/kg at the end of surgery	Desflurane Lidocaïne : 1.5 mg/kg/h Ketamine : 0.25 mg/kg/h	8mg i.v Dexamethasone	Morphine i.v PCA Lidocaïne 1.5 mg/kg/h for 12 hours paracetamol 1g/6h nefopam 20mg/6h	Opioid side event
Bhardwaj et Al. 2019	OFA (40) OBA (40)	Laparoscopic urological surgery	Dexmedetomidine I : 0.5 µg/kg over 10 min M : 0.1 – 0.3 µg/kg/h Lidocaïne I : 1.5 mg/kg M : 0.1 mg/kg/h	Fentanyl I : 2 µg/kg M : intermittent 0.5 µg/kg bolus	Propofol 50–200 µg/kg/min	8mg i.v Dexamethasone 4mg i.v Ondansetron	75mg i.v diclofenac 1mg i.v. paracetamol Rescue : 100mg i.v Tramadol (additional 50 mg every 30 minutes, max 250mg	Opioid consumption, haemodynamic stability
Bulow et Al. 2007	OFA (15) OBA (15)	Gynaecologic videolaparoscopic surgery	Single 100µg of i.v fentanyl at the induction Dexmedetomidine M : 0.5µg/kg/h	Remifentanil I/M : 0.3µg/kg/min	Propofol TCI : 4.0-5.0µg/ml	None	100mg i.v ketoprofen Rescue 1g i.v Dypirone	Haemodynamic stability, cortisol/glucose level
Choi J.W. et Al. 2016	OFA (32) OBA 1 (31) OBA 2 (30)	Laparoscopic hysterectomy	Dexmedetomidine I : 1 µg/kg over 10 min M : 0.5 µg/kg/h	OBA 1 : Fentanyl I : 1.0 µg/kg M : 0.4 µg/kg/h OBA 2 : Remifentanil I : 1.0 µg/kg M : 0.08 µg/kg/min	Desflurane 6-7% volume	None	30mg i.v ketorolac	Haemodynamic stability, sedation, postoperative pain
Choi E.K. et Al. 2017	OFA (40) OBA (40)	Thyroïdectomy	Dexmedetomidine I : 1 µg/kg over 10 min M : 0.3–0.5 µg/kg/h	Remifentanil I : TCI 4 ng/ml M : TCI of 2-3ng/mL	1.0–2.5% Sevoflurane	None	None	PONV
Cortinez et Al. 2001	OFA (30) OBA (30)	Open gynaecological surgery	Sevoflurane I : 2% M : 0.5±1.0% increments	Remifentanil I : 0.25mg/kg/min M : 0.05±0.1mg/kg/min increment/decrement	Sevoflurane	0.2mg i.v Droperidol with each PCA bolus	Morphine i.v PCA (bolus dose 1mg, 8min lockout)	Opioid consumption, postoperative pain

Curry et Al. 1995	OFA (22) OBA (22)	laparoscopic Electrocautery tubal ligation	Saline I : 1 µg /kg	Fentanyl I : 1 µg /kg	Propofol 200-300 µg/kg/min Isoflurane not exceeding 0.5%.	None	Fentanyl i.v PCA (25 µg bolus dose, 5 min lockout, no dose limit)	Opioid consumption, postoperative pain
Feld et Al. 2006	OFA (10) OBA (10)	Open gastric bypass	Dexmedetomidine I : 0.5µg/kg over 10min M : 0.4µg/kg/h	Fentanyl I : 0.5µg/kg M : 0.5µg/kg/h	Desflurane	None	Morphine i.v PCA	Heamodynamic stability, postoperative pain
Gazi et Al. 2018	OFA (15) OBA (15)	Hysteroscopy	Dexmedetomidine I/M : 0.2-0.7 µg/kg/h	Remifentanil I/M : 0.05-0.5µg/kg/min	2% Fi sevoflurane	0.1 mg/kg i.v Ondansetron	1000 mg i.v Paracetamol	aIntraoperative pain, haemodynamic stability, postoperative pain, side effect
Goyal et Al. 2017	OFA (30) OBA (30)	Breast cancer	Dexmedetomidine I : 1 µg/kg over 10 min M : 0.25 µg/kg/h	Fentanyl I : 2 µg/kg over 10 min M : 0.5 µg/kg/h	Desflurane	None	1mg/kg i.v Diclofenac and 1g i.v Paracetamol Rescue : 1mg/kg i.v tramadol and 10mg i.v Pethidine (max 50 mg) as second rescue analgesia	Opioid consumption, haemodynamic stability, halogene requirement, recovery
Hakim et Al. 2019	OBA (40) OFA (40)	Gynecological laparoscopic surgery	Dexmedetomidine I : 0.6 µg/kg over 5 min M : 0.2µg/kg/h ±0.1µg/kg/h	Fentanyl I : 1 µg/kg over 5 min M : 0.5µg/kg/h ±0.1µg/kg/h	Propofol I/M : 5–10 mg/kg/h	None	30mg i.v Ketorolac, and 1g i.v acetaminophen every 8 h Rescue : 0.5 µg/kg i.v Tramadol	Recovery
Hontoir et Al. 2016	OFA (33) OBA (33)	Breast cancer surgery	Clonidine I : 0.2 µg/kg	Remifentanil I/M : TCI	Sevoflurane	4mg i.v Ondansetron	1g i.v Paracetamol and 75mg i.v Diclofenac and 0.03mg/kg i.v Piritramide Piritramide i.v PCA (2 mg bolus, 10min lockout interval, maximum dose of 20mg/4h)	Recovery, opioid consumption, postoperative pain
Hossam et Al. 2017	OFA (30) OBA (30)	Arthroscopic shoulder surgery	Dexmedetomidine I : 1µg/kg over 10min M : 0.5µg/kg/h	Fentanyl I : 1µg/kg M : 0.5µg/kg/h	1.5% isoflurane	None	Rescue : 0.04 mg/kg i.v morphine bolus	Haemodynamic stability, postoperative pain, sedation
Hwang et Al. 2017	OFA (20) OBA (20)	Posterior lumbar interbody fusion	Dexmedetomidine I/M : 0.01-0.02µg/kg/min	Remifentanil I/M : 0.01-0.02 µg/ kg/min	propofol I/M : 3-12 mg/kg/h	0.3mg i.v Ramosetron	i.v Hydromorphone PCA (background rate of 0.12mg/h, 0.12mg bolus	Opioid consumption,

							dose, 10min lockout interval of 10 minutes Rescue : 1 µg/kg i.v Fentanyl or 50 mg i.v Tramadol	postoperative pain, PONV
Inoue et Al. 2005	OFA (25) OBA (25)	Cervical spine surgery	Single 100µg i.v fentanyl bolus at the induction M : 1.5%-2.5% Fet Sevoflurane	Fentanyl I : 100µg i.v M : 50µg intermittent bolus + 0.5-1.0% Fet Sevoflurane	Sevoflurane	None	50mg i.v Flurbiprofen axetil Rescue : 50µg i.m Fentanyl	Recovery
Javaherforoo-shzadeh et Al. 2018	OFA (30) OBA (30)	Lumbar discopathy surgery	Fentanyl I : 2 to 3µg/kg Dexmedetomidine M : 0.3 to 0.7µg/kg/h	Fentanyl I : 2 to 3µg/kg Remifentanil M : 0.1 to 1.0µg/kg/h	Propofol 50 to 100µg/kg/min	None	None	Haemodynamic stability, blood loss
Jung et Al. 2011	OFA (25) OBA (25)	Elective total laparoscopic hysterectomy	Dexmedetomidine I : 1 µg/kg over 10 min M : 0.2-0.7 µg/kg/h	Remifentanil I : 0.8-1.2 µg/kg over 1 min M : 0.05-0.1 µg/kg/h	6-7 vol.% of desflurane	None	30mg i.v ketorolac	heamodynamic stability, sedation, postoperative pain
Kataria et Al. 2016	OFA (30) OBA (30)	Laparoscopic cholecystectomy	Dexmedetomidine I : 1 µg/kg M : 0.2 µg/kg	Fentanyl I : 1 µg/kg M : 0.2 µg/kg intermittent bolus.	Isoflurane	None		haemodynamic stability
Katz et Al. 1996	OFA (15) OBA (15)	Hysterectomy	Saline	Alfentanil I : 30ug/kg M : 10-20ug/kg every hour	Isoflurane	None	Morphine i.v PCA (1,5-2.0mg bolus, 5-7min lockout intervalle, maximum dose of 30 mg/4h)	Opioid consumption, postoperative pain
Lee C. et Al. 2011	OFA (30) OBA (30)	Tonsillectomy	Saline	Remifentanil I : 1 µg/kg M : 0.1 µg/kg/min ± 0.05 µg/kg/min increment	Sevoflurane OFA titrated on BIS OBA 1 MAC	None	Rescue : 25mg i.v Pethidine 25 mg (VAS ≥ 4) or 30mg i.v Ketorolac (VAS ＜ 4)	Opioid consumption, postoperative pain
Lee J. et Al. 2013	OFA (32) OBA (34)	Endoscopic sinus surgery	Dexmedetomidine I : 1 µg/kg over 10min M : 0.4-0.8 µg/kg/h.	Remifentanil I : 1 µg/kg over 1 min M : 0.2-0.4 µg/kg/min	5 to 7 vol% Desflurane	None	Rescue : 30mg i.v ketorolac tromethamine 30 mg	Haemodynamic stability
Mansour et Al. 2013	OFA (15) OBA (13)	Laparoscopic sleeve surgery	Ketamine I : 0.5 mg/kg M : 0.5 mg/kg/h (IBW)	Fentanyl I : 2-5 µg/kg M : 0.025-0.25µg /kg/min (IBW)	2-4% sevoflurane	50mg i.v Ranitidine + 10mg i.v Metoclopramide + 8mg i.v Dexamethasone	OFA : 1g/6h i.v Paracetamol and 75mg/12h i.m and 60-100mg/12h i.v and Tramadol i.v PCA (10mg bolus, 6min lock-out interval, no basal infusion).	Haemodynamic stability

							Rescue : 2-4m/2h i.v Morphine OBA : 1g/6h i.v Paracetamol and Fentanyl i.v PCA (10µg bolus, 6min lock-out interval)	
Mogahead 2017	OFA (40) OBA (40)	Laparoscopic cholecystectomy	Dexmedetomidine I : 0.7 ug/kg over 10 min M : 0.4 ug/kg/h	Remifentanil I : 0.7 ug/kg over 10 min M : 0.2 ug/kg/h	1-1.5MAC Sevoflurane	8mg i.v Dexamethasone and 4mg i.v Ondansetron	Rescue : 25 mg i.v fentanyl	Expiratory fraction Sevoflurane concentration
Mulier et Al. 2018	OFA (25) OBA (25)	laparoscopic bariatric surgery	Dexmedetomidine I : 0.5 mg/kg over 10 min M : 0.25 - 1 mg/ kg/h Ketamine I : 0.25 mg/kg Lidocaine I : 1.5 mg/kg M : 1.5-3 mg/kg/h	Sufentanil I : 0.5 mg/kg M : 0.25-1 mg/kg/ (IBW)	Sevoflurane	None	2g i.v Paracetamol then 1g/6h And Morphine i.v PCA (2mg bolus, 5min lock-out interval, no basal infusion)	Haemodynamic stability, opioid consumption, recovery
Ryu et Al. 2019	OFA (40) OBA (40)	Middle ear surgery	Magnesium sulfate I : 50mg/kg over 10 min M : 15mg/kg/h	Remifentanil I : TCI 4ng/ml M : TCI 3-4 ng/ml	Sevoflurane	None	30mg i.v Ketorolac	Haemodynamic stability, postoperative pain
Sahoo et Al. 2016	OFA (80) OBA (80)	Laparoscopic gynaecological surgery	Dexmedetomidine I : 0.01µg/kg/min M : 0.05 µg/kg/min	Remifentanil I : 0.01 µg/kg/min M : 0.05µg/kg/min	Propofol 3-12 mg/kg/h	0.3mg i.v Ondansetron	Morphine i.v PCA (2 mg bolus, background rate of 1 mg/h, 10min lockout interval) Rescue : 1 µg/kg i.v Fentanyl or 50mg i.v Tramadol	Opioid consumption, postoperative pain, PONV
Salman et Al. 2019	OFA (30) OBA (30)	Ambulatory gynaecologic laparoscopic surgery	Dexmedetomidine I : 1 µg/kg over 10min M : 0.4 µg/kg/h	Remifentanil I : 1 µg/kg over 10 min M : 0.2 µg/kg/min	6% desflurane	None	1g p.o Paracetamol Rescue : 30-40 µg /kg morphine	Haemodynamic stability, opioid consumption, postoperative pain, PONV, recovery
Senol Karatas et Al. 2015	OFA (16) OBA 1 (16) OBA 2 (16) OBA 3 (16)	major abdominal surgery	Saline I : 5 cc bolus M : 10 cc/h	OBA 1 : Remifentanil I : 1µg/kg M : 0.25 µg/kg/min OBA 2 : Alfentanil I : 10 µg/kg	1 MAC desflurane	None	1 g i.v Paracetamol and 1 mg/kg i.v Mepiridine Meperidine i.v PCA (15mg bolus dose, 8min lockout time)	Opioid consumption

				M : 0.50 µg/kg/min OBA 3 : Morphine I : 0.1 mg/kg M : 0.02 mg/kg/h				
Subasi et Al. 2017	OFA (20) OBA (20)	Laparoscopic cholecystectomy	Single 1µg/kg i.v Fentanyl bolus at the induction Dexmedetomidine M : 0.5µg/kg/h lowered to 0.3 µg/kg/h after 5 minute of infusion	Fentanyl I : 1µg/kg M : 0.5µg/kg/h lowered to 0.3 µg/kg/h after 5 minute of infusion	Propofol 150 µg/kg/min	None	Morphine i.v PCA (1mg bolus dose, 20min lockout interval)	Haemodynamic stability, opioid consumption, postoperative pain, recovery
Techanivate et Al. 2012	OFA (20) OBA (20)	Outpatient gynaecologic laparoscopy	Dexmedetomidine I : 0.5 µg/kg no maintenance	Fentanyl I : 0.5 µg/kg no maintenance	desflurane	None	1g p.o paracetamol Rescue : 25µg i.v Fentanyl.	Postoperative pain
Toleska et Al. 2019	OFA (30) OBA (30)	Laparoscopic cholecystectomy	Ketamine I : 0.5 mg/kg Lidocaïne M : 2 mg/kg/h Magnesium sulphate M : 1.5 g/h	Fentanyl : I : 2µg/kg M : intermittent Fentanyl bolus	0.7-1 MAC Sevoflurane	0.1 mg/kg i.v Dexamethasone	1g i.v Paracetamol, and 2.5g Metamizole (OBA) Rescue : 100mg i.v Ketoprofen or 100mg i.v Trodon	Opioid consumption, postoperative pain
Tverskoy et Al. 1994	OFA 1 (9) OFA 2 (9) OBA (9)	Elective transabdominal hysterectomy	OFA 1 : ketamine I : 2 mg/kg M : 20 pg/kg/min OFA 2 : isoflurane only	Fentanyl I : 5 pg/kg M : 0.02 pg/kg/min	Isoflurane	None	First 9h : i.v meperidine on demand 9 to 24h : 50mg/4h i.m Meperidine ± 25 mg on demand > 24h : 0.5g/4h p.o Dipyrone	Postoperative pain

OFA : Opioïd-free anaesthesia ; OBA : Opioïd based anaesthesia ; PONV : Postoperative nausea and vomiting ; I : induction period ; M : maintenance period ; i.v : intravenous ; i.m : intramuscular ; PCA : patient-controlled analgesia ; TCI : target-controlled infusion

Supplementary data 2 : Subgroup analysis

Subgroup analysis for morphine at 24h

Outcomes	Number of trials	Number of participants	SMD Random effect [95% CI]	Heterogeneity (I^2)	Heterogeneity (I^2) – Test for subgroup differences
Active drug	5	200	-3.84 [-5.03, -2.65]	0%	91%
Saline	5	227	0.84 [-1.70, 3.39]	66%	
Strict OFA	7	327	-1.58 [-3.64, 0.48]	72%	0%
Opioid during induction	2	100	-2.86 [-6.20, 0.48]	33%	
PCA	7	340	-2.65 [-5.20, -0.11]	74%	74%
No PCA	2	87	0.10 [-3.55, 3.76]	66%	
Propofol	2	77	-4.17 [-6.19, -2.15]	19%	74%
halogenated agents	7	350	-0.89 [-2.76, 0.99]	62%	

Subgroup analysis for pain at 24h

Outcomes	Number of trials	Number of participants	SMD Random effect [95% CI]	Heterogeneity (I^2)	Heterogeneity (I^2) – Test for subgroup differences
Active drug	9	547	0.02 [-0.88, 0.91]	94%	0%
Saline	2	100	0.23 [-0.28, 0.74]	74%	
Strict OFA	9	547	0.05 [-0.70, 0.79]	93%	0%
Opioid during induction	2	100	-0.25 [-0.43, -0.06]	0%	
PCA	8	500	-0.46 [-0.98, 0.06]	86%	71%
No PCA	3	147	1.04 [-0.44, 2.53]	95%	
Propofol	3	237	-1.00 [-2.61, 0.61]	91%	48%
Halogenated agents	8	410	0.23 [-0.45, 0.91]	92%	

Subgroup analysis for nausea at PACU

Outcomes	Number of trials	Number of participants	RR Random effect [95% CI]	Heterogeneity (I^2)	Heterogeneity (I^2) – Test for subgroup differences
Active drug	18	1417	0.45 [0.37, 0.55]	13%	0%
Saline	2	104	0.57 [0.36, 0.90]	0%	
Strict OFA	17	1371	0.31 [0.22, 0.43]	12%	15%
Opioid during induction	3	150	0.52 [0.19, 1.47]	23%	
PCA	7	717	0.37 [0.26, 0.52]	12%	71%
No PCA	13	804	0.31 [0.21, 0.46]	15%	
Propofol	7	526	0.32 [0.20, 0.50]	10%	15%
Halogenated agents	13	995	0.35 [0.26, 0.48]	23%	