(Acta Anaesth. Belg., 2021, 72, 115-119)

Effects of intravenous lidocaine on alfentanil consumption during procedural sedation for colonoscopy in patients with inflammatory bowel disease: a randomized controlled trial

T.T.J. Aalbers (*), S.A.S. van den Heuvel (*), E.M. Bronkhorst (**), A.A.J. van Esch (***), G.J. Scheffer (*), M. Vaneker (*)

Abstract: *Background*: Procedural sedation and analgesia (PSA) is used during colonoscopy to facilitate the procedure and relieve patient's discomfort. The foremost risk of PSA is respiratory depression. Lidocaine could be a promising additional analgesic in IBD patients to minimise side effects of PSA.

Objective: Our primary objective was to investigate whether i.v. lidocaine reduces the amount of alfentanil used during PSA in IBD patients. Additionally, we investigated whether lidocaine reduces cardiorespiratory incidents and the amount of propofol required during the procedure.

Design: A randomized, double-blind, placebo controlled study.

Setting: Single-center study from November 2016 to December 2018.

Methods: Seventy-six patients with IBD, ASA 1 or 2, between 18 and 65 years, scheduled for colonoscopy with PSA were included. Exclusion criteria were: pregnancy, emergency colonoscopy, allergies for study medication, rhythm disorders, cardiomyopathy, BMI < 18 kg m^{-2}, BMI > 35 kg m^{-2}, obstructive sleep apnea syndrome and uncontrolled hypertension. Patients received lidocaine 1.5 mg kg^{-1} followed by a continuous infusion of 2 mg kg^{-1} h^{-1} (intervention group, *n*=38) or 0.9% saline in equivalent volumes (control group, *n*=38) during colonoscopy.

Main outcome measures: Amount of alfentanil and propofol used during the interventional procedure. Cardiorespiratory events as defined in methods during the colonoscopy.

Results: There was a not statistically significant reduction in the use of alfentanil [327 µg (95%CI=-31-505, p=0.082)] and propofol [39 mg (95%CI=-5-83, p=0.083)] in the lidocaine group compared with the control group. Ten patients (26%) in the control group and 8 patients in the lidocaine group (21%) experienced a period of hypoxia (p=0.788). In both groups, no periods of hypotension were noted.

Conclusion: Our investigation has shown a trend for reduced alfentanil and propofol consumption in patients receiving lidocaine during colonoscopy under sedation. The differences were not statistically significant. Lidocaine did not reduce the incidence of cardiorespiratory events.

Keywords: Deep sedation; Lidocaine, Alfentanil, colonoscopy

Introduction

Colonoscopy is a commonly performed procedure to diagnose or follow up inflammatory bowel disease (IBD) such as Crohn's disease and ulcerative colitis. However, colonoscopy can be an uncomfortable and painful procedure, especially in patients with IBD because of an increased visceral afferent hypersensitivity. Therefore there is an increased need of analgesics in these patients (1). Procedural sedation and analgesia (PSA) is used during colonoscopy to facilitate the procedure and relieve patient's discomfort (2).

Propofol combined with a short-acting opioid is frequently used for PSA, due to its fast onset, improved patient satisfaction, reduced pain scores and quicker recovery (3-5). The foremost risk of PSA is pharmacologically induced respiratory depression (6, 7). There is a continuous search for ways of minimising this risk.

T.T.J. Aalbers, MPA; S.A.S. van den Heuvel, PhD; E.M. Bronkhorst, PhD; A.A.J. van Esch , PhD; G.J. Scheffer, PhD; M. Vaneker PhD

(*) Department of Anesthesiology, Pain and Palliative Medicine, Radboud University Medical Centre, Nijmegen, Netherlands

(**) Department of Health Evidence, Radboud University Medical Centre, Nijmegen, Netherlands

(***) Department of Gastroenterology and Hepatology, Radboud University Medical Centre, Nijmegen, Current position, Department of gastroenterology and hepatology, Gelre Hospital, Apeldoorn, Netherlands

Corresponding author: Twan Aalbers, Dpt off Anesthesiology, Pain and Palliative Medicine, Radboud University Medical Centre, in-house postal number 717, P.O. Box 9101, 6500 HB Nijmegen, Netherlands Phone: +31243614406
Email: twan.aalbers@radboudumc.nl

Paper submitted on Oct 16, 2020 and accepted on Jun 19, 2021
Conflict of interest: None

Lidocaine has a proven analgesic and opioid-sparing effect on the use of opioids during abdominal surgery (8, 9). It reduces a hyperinflammatory response and inhibits the evoked and spontaneous neuronal activity, which is activated by colorectal distension (10, 11). Overall there is an opioid-sparing effect of 0% up to 25% with a maximum of 35% (12-14). One study showed that lidocaine reduces the use of propofol during colonoscopy, though did not evaluate opioid administration (15). Based on these studies, lidocaine could be a promising additional analgesic in IBD patients to minimize side effects on PSA.

The aim of our study was to investigate whether lidocaine is able to reduce the alfentanil consumption in IBD patients undergoing PSA for elective colonoscopy. Additionally, we investigated if lidocaine reduces the incidence of adverse cardiorespiratory events, the amount of propofol required during the procedure and postprocedural pain.

Methods

This double-blind randomized controlled trial was performed at the endoscopy unit of the Radboud University Medical Centre (Nijmegen, The Netherlands).

The study had been approved by the regional ethics committee CMO Arnhem-Nijmegen, The Netherlands (chairperson R. Dekhuijzen) on September 1, 2016 (METC nr 2016-2624). All the procedures were performed in accordance with the Declaration of Helsinki.

Patients

Potential participants were assessed for eligibility during the pre-operative anesthesia assessment. Patients with IBD, ASA 1 or 2, between 18 and 65 years, scheduled for colonoscopy with PSA were eligible for inclusion. Exclusion criteria defined as: pregnancy, emergency colonoscopy, allergies for study medication, previously diagnosed rhythm disturbances *i.e*. first, second or third degree AV block, Brugada syndrome, cardiomyopathy, BMI <18 kg m^{-2}, BMI > 35 kg m^{-2}, obstructive sleep apnea syndrome and uncontrolled hypertension.

Study protocol

After obtaining written informed consent, patients were randomly assigned to either lidocaine or placebo treatment in a 1:1 ratio by an independent research team. The randomization process was conducted by drawing sealed envelopes that contained the word lidocaine or saline written on a piece of paper. The first treatment that was drawn was allocated to the first subject, the second treatment drawn was allocated to the second subject and so on. Extra envelopes were available in case of patients dropping out of the study before completion. The randomization details were not revealed until the end of the study. The inclusion was stopped at the moment that the 76th patient received either lidocaine or placebo. The pharmacists, who prepared the solutions, were unaware of the randomization codes. Study medication delivered in identically appearing 50 ml syringes at the endoscopy unit. Lidocaine was administered intravenously with a bolus of 1.5 mg kg^{-1} followed by a continuous infusion of 2 mg kg^{-1} h^{-1} ideal body weight. This is a commonly used dosage in abdominal surgery for analgesia (9, 11). The placebo group received 0.9% saline in equivalent volumes.

All patients were monitored with non-invasive blood pressure, electrocardiography, pulse oximetry and capnography during PSA. Supplemental oxygen (3 l min^{-1}) was administered by a nasal cannula. Procedural sedation was performed by the same health care provider in all the patients. We performed PSA according to a standardized protocol. The Ramsey Sedation Scale score was maintained at 4 and 5. (RSS 0-6; 1 = patient is anxious, 6 = patient is unresponsive)(16). Patients received a bolus propofol of 1 mg kg-1 followed by an infusion of 4.5 mg kg^{-1} h^{-1} ideal body weight. The Ramsey Sedation Scale and reaction on pain stimulus were continuously monitored. If needed, an additional 20 mg bolus of propofol was administered. The Wong Baker Face Scale (WBFS) was used as a supplement to the clinical impression of pain (17, 18). An additional alfentanil dose of 0.25 mg was given when a score of ≥ 4 was observed. (WBFS 0 = no hurts, 10 = hurts worst). After the administration of propofol or alfentanil, a minimum of 2 minutes was allowed to assess the effect before a new dose was administered. At the end of the colonoscopy, the total dose of propofol and alfentanil was registered.

We registered the number of incidents of hypoxia and of hypotension during PSA. Hypoxia was noted when saturation was ≤ 92% and an intervention was needed such as: vigorous tactile stimulation, airway repositioning (jaw thrust, chin lift or head repositioning), suctioning, increased oxygen delivery, oral or nasal airway placement, application of positive pressure or ventilation with bag mask (19). Hypotension was noted when mean

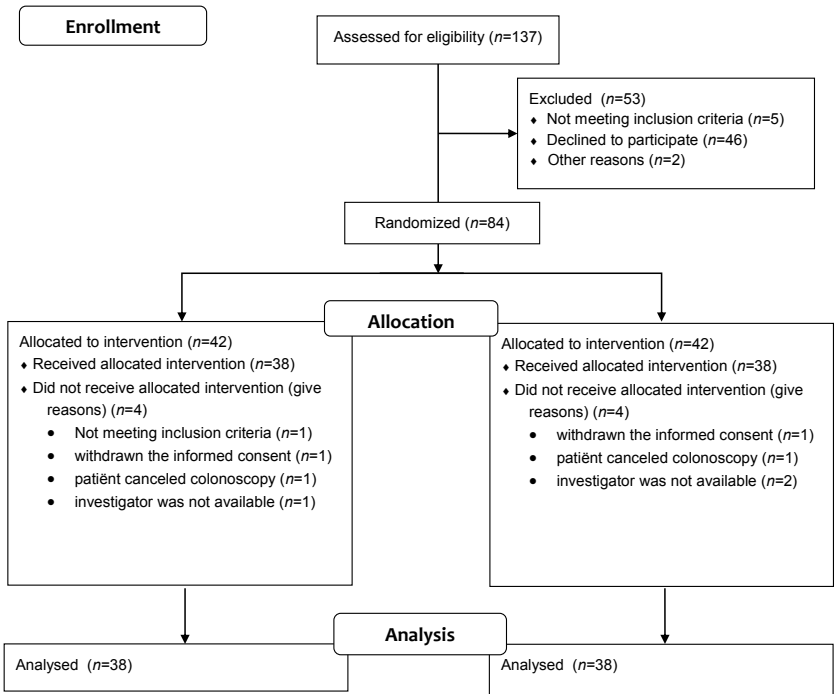

Fig. 1. — CONSORT flowchart

arterial pressure (MAP) < 60 mmHg and 5 mg ephedrine was administered (20).

After colonoscopy, patients remained in the recovery room until the Aldrete score was ≥ 9 for at least 30 minutes (maximum total score is 10; a score of ≥ 9 is required for discharge) (21). Pain was assessed according to a Numeric Rating Scale (NRS 0 -10; 0 = no pain, 10 = worst pain imaginable) when they were fully awake (18).

Additionally, patients were asked if there was any unpleasant recall of the procedure and possible adverse effects of lidocaine such as tinnitus, metallic taste, blurred vision or double vision were registered.

Outcomes

The primary endpoint was the difference between alfentanil dosage in patients with and without lidocaine during the colonoscopy. Additionally we evaluated the difference in propofol dosage, the number of cardiorespiratory adverse events and postprocedural NRS between groups.

Statistical analysis

A dose of 10 μg kg^{-1} alfentanil is commonly used for PSA, in a retrospective analysis of IBD patients who came for a colonoscopy we found an alfentanil consumption of 0.5 and 0.75 mg. According to this the following sample size was calculated (22). An alfentanil dose of 0.625 mg in the placebo group, and 0.25 mg in patients receiving lidocaine, with a standard deviation of 0.58 mg was expected. This leaves us with a *n* of 38 per group, to achieve a 80% chance for the difference of 0.375 mg to be statistically significant with an α of 0.05.

Descriptive statistics are presented as mean ± SD [minimum-maximum], unless stated otherwise. Categorical data were analyzed using Fischer exact test. Continuous data were tested for normal distribution using Kolmogorov-Smirnov test. For normal distribution, data were analyzed using unpaired student t-test. Mann-Whitney U test was used when data were not normally distributed. Statistical analysis was performed using IBM SPSS Statistics V25.0. $P<0.05$ was considered statistically significant.

Results

From November 2016 to December 2018, 137 patients were assessed for enrollment, and 76 were included in the data analysis, 38 for each group. Figure 1 shows the CONSORT flowchart with the excluded patients. Both groups were comparable for age, gender, weight, BMI and duration of PSA (Table 1).

There was a reduction in the use of alfentanil in the lidocaine group of 327 μg compared with the control group. The 95% confidence interval for this reduction is [-31-505] (p=0.082). For the

Table 1

Clinical characteristics

	Placebo, *n*=38	**Lidocaine,** *n*=38
Age (years)	38 ± 11 [21-62]	37 ± 14 [19-65]
Gender (*n*)		
Men	17	15
Women	21	23
Disease (*n*)		
Crohn	31	31
Colitis ulcerosa	7	7
Weight (kg)	76.8 ± 17.1	75.4 ± 13.4
Height (m)	1.74 ± 0.09	1.76 ± 0.09
BMI (kg m^{-2})	25.2 ± 4.3 [18.4-34.2]	24.2 ± 3.1 [18.3-30.7]
Duration of PSA (minutes)	33 ± 10 [18-59]	32 ± 10 [15-57]
Placebo/lidocaine 1% (ml)	20.1 ± 5.9	19.3 ± 3.8

Data are presented as number (*n*) or mean ± SD [range].

Table 2

Outcome Measures

	Placebo	**Lidocaine**	**P value**
Alfentanil (µg)	868 ± 647 [0-2500]	632 ± 519 [0-1750]	0.082
Propofol (mg)	387 ± 106 [222-665]	349 ± 85 [181-556]	0.095
Hypoxia (*n*)	10 (26%)	8 (21%)	0.788
Hypotension (*n*)	0	0	1.000
Postcolonoscopy pain (NRS)	0 [0-8]	0 [0-8]	1.000

Data are presented as number (*n*), mean ± SD [range], or median [range].

use of propofol the reduction was 39 mg, 95% confidence interval = [-5-83] (p=0.083) (Table 2). This reduction of alfentanil and propofol was not statistically significant.

No statistically significant difference in the number of hypoxia incidents between groups was found (p=0.788). Ten patients (26%) in the control group and eight patients in the lidocaine group (21%) experienced a period of hypoxia. No periods of hypotension were noted.

Postprocedural NRS scores were similar in both groups. Thirty-five patients in the control group and 33 patients in the intervention group reported no pain postcolonoscopy. Patients who participated in the study had no side effects on the lidocaine.

Discussion

This randomized controlled trial in IBD patients undergoing PSA for a colonoscopy has shown a reduction in the use of alfentanil and propofol. The differences were not statistically significant. No differences in hypoxia, hypotension and postprocedural pain scores were found.

We found a large interpatient variability in anesthetic requirement, leading to only a tendency for reduced alfentanil and propofol requirements. This variability may be explained by the variation in ways to perform the procedure and the difference in pain sensitivity between patients. Further research is needed in patients with a high pain sensitivity or who previously needed a high dose of alfentanil during a colonoscopy. Although we studied IBD patients, only few patients experienced postprocedural pain and pain scores were low. In our study CO_2 insufflation was used during colonoscopy. CO_2 insufflation induces less postprocedural pain compared with nitrogen due to more rapid absorption (23).

The incidence of cardiorespiratory events were similar in both groups. Hypoxia secondary to respiratory depression and airway obstruction is the most frequent complication of PSA during colonoscopy (6, 19). In our study 24% of the patients have undergone a period of hypoxia, which is comparable with most other studies (24).

None of the patients in our study experienced a period of hypotension, which is a relative rare adverse event during PSA, (6, 19) especially in a study population without cardiovascular comorbidity. However, the reporting of sedation-related complications has been subject to substantial variability due to differences in PSA depth and criteria for hypoxia or hypotension. A recent study suggested advice for evaluating sedation-related complications (6).

Our study has some limitations. Our sample size calculation was too optimistic which resulted in an underpowered study. Procedures were performed by several endoscopists and we did not include technical difficulty as a variable since this can be related to an uncomfortable procedure (25). As in common daily practice, administration of alfentanil was based on the clinical impression by the same operator, in order to reduce bias. In future studies it would be interesting to use nociception monitors which can increase accuracy of pain evaluation. This could have influenced our conclusions regarding the effect of lidocaine on alfentanil consumption.

Conclusion

There was a not statistically significant reduction in alfentanil and propofol consumption in patients receiving lidocaine during colonoscopy under PSA in IBD patients. Lidocaine did not reduce the incidence of cardiorespiratory events or postprocedural pain. Based on these results, standard administration of lidocaine may be helpful in patients with high need for alfentanil during colonoscopy, but further investigation is needed.

References

1. Denters MJ, Schreuder M, Depla AC, Mallant-Hent RC, van Kouwen MC and Deutekom M, et al. 2013. Patients' perception of colonoscopy: patients with inflammatory bowel disease and irritable bowel syndrome experience the largest burden. Eur J Gastroenterol Hepatol. 25(8):964-72.
2. Lu Y, Hao LX, Chen L, Jin Z and Gong B. 2015. Systematic review and meta-analysis of patient-controlled sedation versus intravenous sedation for colonoscopy. Int J Clin Exp Med. 8(11):19793-803.
3. Michel Foehn ER. 2015. Adult and pediatric anesthesia/sedation for gastrointestinal procedures outside of the operating room. Curr Opin Anaesthesiol. 28(4):469-77.
4. Schroeder C, Kaoutzanis C, Tocco-Bradley R, Obear J, Welch KB and Winter S, et al. 2016. Patients Prefer Propofol to Midazolam Plus Fentanyl for Sedation for Colonoscopy: Results of a Single-Center Randomized Equivalence Trial. Dis Colon Rectum. 59(1):62-9.
5. Wang D, Chen C, Chen J, Xu Y, Wang L and Zhu Z, et al. 2013. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. PLoS One. 8(1):e53311.
6. Roback MG, Green SM, Andolfatto G, Leroy PL and Mason KP. 2018. Tracking and Reporting Outcomes Of Procedural Sedation (TROOPS): Standardized Quality Improvement and Research Tools from the International Committee for the Advancement of Procedural Sedation. Br J Anaesth. 120(1):164-72.
7. Conway A, Douglas C and Sutherland J. 2015. Capnography monitoring during procedural sedation and analgesia: a systematic review protocol. Syst Rev. 4:92.
8. McCarthy GC, Megalla SA and Habib AS. 2010. Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. Drugs. 70(9):1149-63.
9. Kranke P, Jokinen J, Pace NL, Schnabel A, Hollmann MW and Hahnenkamp K, et al. 2015. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery. Cochrane Database Syst Rev. (7):CD009642.
10. Ness TJ. 2000. Intravenous lidocaine inhibits visceral nociceptive reflexes and spinal neurons in the rat. Anesthesiology. 92(6):1685-91.
11. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M and Steegers MA, et al. 2016. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 20(5):655-74.
12. Weibel S, Jokinen J, Pace NL, Schnabel A, Hollmann MW and Hahnenkamp K, et al. 2016. Efficacy and safety of intravenous lidocaine for postoperative analgesia and recovery after surgery: a systematic review with trial sequential analysis. Br J Anaesth. 116(6):770-83.
13. Abdelrahman I, Steinvall I, Elmasry M and Sjoberg F. 2020. Lidocaine infusion has a 25% opioid-sparing effect on background pain after burns: A prospective, randomised, double-blind, controlled trial. Burns. 46(2):465-71.
14. Koppert W, Weigand M, Neumann F, Sittl R, Schuettler J and Schmelz M, et al. 2001. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg. 98(4):1050-5, table of contents.
15. Forster C, Vanhaudenhuyse A, Gast P, Louis E, Hick G and Brichant JF, et al. 2018. Intravenous infusion of lidocaine significantly reduces propofol dose for colonoscopy: a randomised placebo-controlled study. Br J Anaesth. 121(5):1059-64.
16. Avci S, Bayram B, Inanc G, Goren NZ, Oniz A and Ozgoren M, et al. 2019. Evaluation of the compliance between EEG monitoring (Bispectral IndexTM) and Ramsey Sedation Scale to measure the depth of sedation in the patients who underwent procedural sedation and analgesia in the emergency department. Ulus Travma Acil Cerrahi Derg. 25(5):447-52.
17. Garra G, Singer AJ, Taira BR, Chohan J, Cardoz H and Chisena E, et al. 2010. Validation of the Wong-Baker FACES Pain Rating Scale in pediatric emergency department patients. Acad Emerg Med. 17(1):50-4.
18. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW and Loge JH, et al. 2011. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 41(6):1073-93.
19. Bhatt M, Kennedy RM, Osmond MH, Krauss B, McAllister JD and Ansermino JM, et al. 2009 Consensus-based recommendations for standardizing terminology and reporting adverse events for emergency department procedural sedation and analgesia in children. Ann Emerg Med. 53(4):426-35 e4.
20. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A and Rodseth RN, et al. 2013. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology. 119(3):507-15.
21. Aldrete JA. 1995. The post-anesthesia recovery score revisited. J Clin Anesth. 7(1):89-91.
22. Turk HS, Aydogmus M, Unsal O, Koksal HM, Acik ME, and Oba S. 2013. Sedation-analgesia in elective colonoscopy: propofol-fentanyl versus propofol-alfentanil. Braz J Anesthesiol. 63(4):352-7.
23. Kim HG. 2016. Painless Colonoscopy: Available Techniques and Instruments. Clin Endosc. 49(5):444-8.
24. Waugh JB, Epps CA and Khodneva YA. 2011. Capnography enhances surveillance of respiratory events during procedural sedation: a meta-analysis. J Clin Anesth. 23(3):189-96.
25. Park DI, Kim HJ, Park JH, Cho YK, Sohn CI and Jeon WK, et al. 2007. Factors affecting abdominal pain during colonoscopy. Eur J Gastroenterol Hepatol. 19(8):695-9.