

PRE-SURGICAL CAUDAL BLOCK AND INCIDENCE OF POSTOPERATIVE NAUSEA AND VOMITING AFTER PEDIATRIC ORCHIOPEXY

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Abstract

Background: The primary aim of studies comparing pediatric caudal block with alternative techniques has always been to assess pain relief as the primary outcome, while the results about nausea/retching/vomiting are either missing or incomplete or relegated to secondary outcome. *Objectives:* To compare pre-surgical caudal blocks with post-surgical incisional field blocks in terms of whether pre-surgical caudal block would reduce the incidence of post-operative nausea/retching/vomiting in pediatric patients undergoing testicular surgery.

Materials and Methods: Boys aged 8-years or less (i.e., including infants) presenting for orchiopexy at our children's hospital were included in our prospective randomized research study. Pre-surgical caudal block participants received a standard caudal block with 1ml/kg 0.25% bupivacaine solution after induction of anesthesia but before initial skin incision while post-surgical incisional field block participants received a standard incisional field block with 1ml/kg 0.25% bupivacaine after completion of surgical procedure. The following were compared between the two groups: age, body mass index, durations of anesthesia and surgery, side and site of testicular surgery and location of incision, postoperative nausea/retching/vomiting scores and use of anti-emetics and analgesics as elicited on follow-up telephone calls to the parents on first and second postoperative days..

Results: A total of 90 participants' data was analyzed with 45 patients in each group. Although statistically insignificant ($p=0.37$), there was a clinically relevant less incidence of analgesics' use among caudal block group participants (62%) compared to post-surgical incisional field block

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group participants (73%). Eighty-percent participants in caudal block group did not report nausea/retching/vomiting while only 64% participants in post-surgical incisional field group did not report nausea/retching/vomiting ($P=0.16$). Even among the participants who were taking emetogenic codeine, decreased incidence of nausea/retching/vomiting among caudal block group participants (18%) compared to post-surgical incisional field block group participants (42%) was clinically relevant despite being statistically insignificant ($P=0.37$). Finally, caudal block significantly decreased the incidence of nausea/retching/vomiting among those participants who had undergone bilateral scrotal and/or inguinal incisions ($P=0.04$) even when such surgeries had significantly longer duration ($P<0.001$) compared to the surgeries with unilateral scrotal incision.

Conclusion: On the first postoperative day among boys who had undergone bilateral scrotal and/or inguinal incisions for orchiopexy, a pre-surgical caudal block significantly decreased the incidence of nausea/retching/vomiting compared to post-surgical incisional field block.

Keywords: Postoperative Nausea And Vomiting; Caudal Block; Incisional Field Block; Pediatric Orchiopexy; Antiemesis.

Introduction

Caudal block has evolved as standard of care for pediatric patients undergoing testicular surgeries¹⁻⁶. The primary aim of studies comparing pediatric caudal block with alternative techniques has always been to assess pain relief as the primary outcome⁷⁻¹⁰, while the results about nausea/retching/vomiting are either missing or incomplete or relegated to secondary outcome. Bansal et al. demonstrated paravertebral block-induced reduction in nausea/vomiting among breast surgery patients¹¹. This inspired publication of personal opinion by a co-author of our current study – DG – in 2012 proposing and making the case for antiemetic role of regional blocks, such as caudal block, performed preemptively before surgical manipulation of organs¹². Thereafter, our team deemed it appropriate to evaluate the effects of caudal block on incidence and severity of nausea/retching/vomiting as the primary outcome presuming that caudal block can

interrupt autonomic and somatic neural outflow from surgically manipulated testes.

The objective for this prospective study was to compare pre-surgical caudal blocks (performed by anesthesiologists) with post-surgical incisional field blocks (performed by surgeons) in terms of whether pre-surgical caudal block would reduce the incidence of post-operative nausea/retching/vomiting in pediatric patients undergoing testicular surgery.

Materials and Methods

After institutional review board approval and written informed parental consent with additional oral assent from 7-8 year-olds themselves, boys aged 8-years or less (i.e., including infants) presenting for orchiopexy at our children's hospital were included in our prospective randomized double-blind research study to compare the anti-emetic effects of pre-surgical caudal blocks with post-surgical incisional field blocks. Only boys aged 8-years or less who presented for orchiopexy with or without orchiectomy/inguinal hernia repair/hydrocelectomy were included in our study. Patients who presented for laparoscopic orchiopexy were excluded. Other exclusion criteria were: parental refusal for blocks (pre-surgical caudal or post-surgical incisional field), history of hypersensitivity to local anesthetics, and patient pathophysiology contraindicating caudal block placement such as local site skin infection, coagulopathy, spine abnormalities and unstable hemodynamics.

Based on a computer generated number list, research participants were randomized into one of two groups. Group 1 (Pre-surgical caudal block): After induction of anesthesia but before initial skin incision, research participant received a standard caudal block with 1ml/kg 0.25% bupivacaine solution limiting maximum dose to 20ml. Group 2 (Post-surgical incisional field block): After completion of surgical procedure, research participant received a standard incisional field block with 1ml/kg 0.25% bupivacaine solution limiting maximum dose to 20ml.

A standard anesthesia technique was used for all research participants. For standard caudal block after the induction of anesthesia and endotracheal

intubation for maintenance of general inhalational anesthesia, the research participant was placed in the left lateral decubitus position with both knees apposing his chest. An assistant helped in sustaining this position. A short bevel 22-gauge 5 cm needle attached to medication filled 20ml syringe (maximum dose of 0.25% bupivacaine being 20ml) was used for injection. A longitudinal ultrasonographic view of the caudal space with hockey stick probe was achieved to appreciate the sacral hiatus between the two sacral cornua. Under sterile conditions, the needle was advanced to the caudal space just anterior to the sacral hiatus. At the entry inside the caudal space, a distinct pop was appreciated and the spread of medication in caudal space per ultrasonographic view was recorded as successful caudal block.

For standard post-surgical incisional field block after completion of surgical procedure, local subcutaneous infiltration of the medication was completed along the open skin margins of the inguino-scrotal incision with 25-gauge needle attached to 20ml syringe (maximum dose of 0.25% bupivacaine being 20ml).

As our data collection was focused primarily on eliciting blocks' anti-emetic effects (if any) in contrast to prior studies primarily eliciting blocks' analgesic effects, only following were observed, recorded and compared between the two groups: age, body mass index, durations of anesthesia and surgery, side and site of testicular surgery and location of incision, postoperative nausea/retching/vomiting scores and use of anti-emetics and analgesics as elicited on follow-up telephone calls to the parents on first and second postoperative days. Study participation was deemed as completed after telephone follow-up calls.

Postoperative nausea/retching/vomiting score was adapted from Bhatnagar et al¹³.

- Score 1: No postoperative nausea/retching/vomiting
- Score 2: Retching only (as young ones cannot vocalize about nausea)
- Score 3: Vomiting once
- Score 4: Multiple Vomiting(s)

Statistical Analysis

Chi Square tests and Fisher exact test compared proportions while analysis of variance compared continuous data to elicit the significance level at $P < 0.05$. Regarding the primary outcome, it was hypothesized that post-surgical incisional field block group would have 70% incidence of nausea/retching/vomiting while caudal block group would have 40% incidence of nausea/retching/vomiting. Therefore, for this hypothesized medium effect 30% reduction in incidence of nausea/retching/vomiting with caudal block, 56 research participants were required in each group to achieve statistical power of 90%. The calculated sample size was rounded up to 60 research participants in each group to accommodate the unexpected exclusion of research participants from the final analysis.

Results

Over a three year time period (2013-2016), a total of 120 research participants were consented. Among them, a total of 30-participants were excluded from the final analysis: 13-participants had consent form discrepancies; 12-participants required changes in peri-operative methods beyond the approved research methods; and 5-participants had incomplete telephone data collection. For the final analysis, 90 participants' data was available with 45 participants in each group with achievable statistical power remaining $> 80\%$ despite excluded participants. Table 1 presents the summary data of these participants. Caudal blocks were completed in 1-attempt (median); however, only 20% participants had documented evidence of ultrasound confirmation plus clinical evidence confirming effective caudal block. Although statistically insignificant ($p = 0.37$), there was a clinically relevant less incidence of analgesics' use among caudal block group participants (62%) compared to post-surgical incisional field block group participants (73%) (Table 2). As shown in Table 3, 80% participants in caudal block group did not report nausea/retching/vomiting while only 64% participants in post-surgical incisional field group did not report nausea/retching/vomiting ($P = 0.16$). Even among the participants who were

taking emetogenic codeine, decreased incidence of nausea/retching/vomiting among caudal block group participants (18%) compared to post-surgical incisional field block group participants (42%) was clinically relevant despite being statistically insignificant ($P=0.37$). Finally, caudal block significantly decreased the incidence of nausea/retching/vomiting among those participants who had undergone bilateral scrotal and/or inguinal incisions ($P=0.04$; Statistical Power=60%) even when such surgeries had significantly longer duration ($P<0.001$) compared to the surgeries with unilateral scrotal incision as shown in Table 4.

Discussion

The key findings in our study were that (a) caudal blocks performed after induction of general anesthesia prolonged total anesthesia duration as compared to incisional field blocks performed at the end of surgery, (b) ultrasound use to guide caudal block and to preemptively confirm its efficacy was new for our team precluding its appropriate and confident use by our team¹⁴, (c) codeine use was very common among our pediatric patients before codeine use

Table 1
Demographics and Summary of Patients' Characteristics.

Characteristic	Caudal Block Group (n=45)	Post-Surgical Incisional Field Block (n=45)	P-Value
Age (in months)	43 \pm 30.2	35.8 \pm 30	0.26
Body mass index (kg/m ²)	17.3 \pm 2.9	18.6 \pm 6.2	0.23
Duration of Anesthesia (in minutes)	89.5 \pm 22.2	76.6 \pm 19	0.004
Duration of Surgery (in minutes)	44.8 \pm 19.2	40.8 \pm 17.4	0.3
Difference In Durations of Anesthesia and Surgery (in minutes)	44.7 \pm 12.1	35.8 \pm 8.1	<0.001
Surgery performed bilaterally (%)	22%	16%	0.59
Postoperative nausea vomiting score on first postoperative day overall	1.4 \pm 0.8	1.6 \pm 0.9	0.22
Postoperative nausea vomiting score on first postoperative day when taking codeine for pain	1.3 \pm 0.6 (n=11)	1.8 \pm 1 (n=12)	0.18
Postoperative Nausea Vomiting Score On First Postoperative Day When Taking Only Acetaminophen or Ibuprofen For Pain	1.5 \pm 1.1 (n=17)	1.5 \pm 0.9 (n=21)	0.87
Postoperative nausea vomiting score on first postoperative day when taking no medication for pain	1.3 \pm 0.7 (n=17)	1.7 \pm 0.9 (n=12)	0.21
Postoperative nausea vomiting score on second postoperative day	1 \pm 0 (n=44)	1 \pm 0.3 (n=43)	0.31

Table 2
First Postoperative Day Telephone Call Elicited Frequency of Analgesic Use.

First postoperative day telephone call	Caudal Block Group (n=45)	Post-Surgical Incisional Field Block Group (n=45)	P-Value
Patients Taking Codeine For Pain [n(%)]	11 (24%)	12 (27%)	0.51
Patients Taking Only Acetaminophen or Ibuprofen For Pain [n(%)]	17 (38%)	21 (47%)	
Patients Taking No Medication For Pain [n(%)]	17 (38%)	12 (27%)	
TOTAL [n(%)]	45 (100%)	45 (100%)	

Table 3
First Postoperative Day Telephone Call Elicited Frequency of Nausea/Retching/Vomiting.

First postoperative day telephone call	Percent Patients Reporting Nausea/Retching/Vomiting(s) In Caudal Block Group	Percent Patients Reporting Nausea/Retching/Vomiting(s) In Post-Surgical Incisional Field Block Group	P-Value
Among patients who were taking codeine for pain	18% (n=11)	42% (n=12)	0.37
Among Patients Who Were Taking Only Acetaminophen or Ibuprofen For Pain	24% (n=17)	29% (n=21)	>0.99
Among patients who were taking no medication for pain	18% (n=17)	42% (n=12)	0.22
Overall	20% (n=45)	36% (n=45)	0.16

Table 4
Association of Surgical Incision's Location with Duration of Surgery and First Postoperative Day Nausea/Retching/Vomiting.

Duration of surgery (in minutes)	Caudal Block Group (n=45)	Post-Surgical Incisional Field Block Group (n=45)	P-Value
Unilateral Scrotal Incision	34.6 ±12.6 (n=23)	29.9 ±9.4 (n=20)	0.17
Other Incisions (Bilateral-Scrotal/ Inguino-Scrotal/ Inguinal Incisions)	55.5 ±19.3 (n=22)	49.6 ±17.5 (n=25)	0.28
P-Value	<0.001	<0.001	
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Percent patients reporting nausea/retching/vomiting(s) On first postoperative day	Caudal Block Group (n=45)	Post-Surgical Incisional Field Block Group (n=45)	P-Value
Unilateral Scrotal Incision	30% (n=23)	35% (n=20)	>0.99
Other Incisions (Bilateral-Scrotal/ Inguino-Scrotal/ Inguinal Incisions)	9% (n=22)	36% (n=25)	0.04
P-Value	0.13	>0.99	

became contraindicated for pediatric pain (and cough) management, and (d) compared to incisional field block, decreased incidence of nausea/retching/vomiting with caudal block achieved statistical significance among participants undergoing orchiopey via bilateral scrotal and/or inguinal incisions.

There may be a possible explanation for differences observed between unilateral scrotal incisions vs. bilateral scrotal and/or inguinal incisions (Table 4). Delayed onset of caudal block might have interfered with complete blockade of sacral dermatomal segment neural outflow after unilateral scrotal incisions. Therefore, decreased incidence of nausea/retching/vomiting with caudal block might not have achieved statistical significance among shorter duration testicular surgeries after unilateral scrotal incisions. Contrarily, lumbar dermatomal segment and autonomic neural outflow after inguinal incisions might have been comprehensively blocked with primary spread of caudal block¹⁵. Moreover, by the time of second scrotal incisions, local anesthetics might have secondarily spread craniocaudally to eventually block autonomic and sacral dermatomal segment neural outflow¹⁶.

Unlike the practice of routinely prescribing analgesics to all postoperative patients, anti-emetics were not automatically prescribed to all postoperative patients which precluded the objective assessment of severity of nausea/retching/vomiting in terms of rescue anti-emetic use. Antiemesis is always relegated to secondary importance as compared to analgesia especially because acute postoperative pain has remained very common despite implementing universal postoperative pain management protocols¹⁷⁻²⁰. Although postoperative nausea/retching/vomiting is not as common as pain, it commonly occurs among 30%-80% postsurgical patients²¹. Still anti-emetics are not automatically prescribed to postsurgical patients unlike routine prescriptions for analgesics to postsurgical patients as seen during our study.

Bramwell et al. (1982) reported that 18% inpatients aged 1-12 years vomited 2-8 hours after caudal block for circumcision, inguinal herniotomy or orchiopey¹. Fell et al. (1988) reported that vomiting at home after caudal block (20%) was similar as after wound infiltration (28%) among unilateral inguinal

herniotomy patients⁷. Lafferty et al. (1990) did not investigate the differences in emesis after caudal block or wound instillation (bupivacaine underneath external oblique aponeurosis) for unilateral orchiopey although they reported that wound instillation significantly decreased operation time while providing analgesia equivalent to caudal block². Schindler et al. (1990) did not find any difference in the incidence of early postoperative vomiting (first 4-hours) after caudal block (19%) or wound infiltration (22%) for unilateral inguinal herniotomy⁸. Ho and Keneally (2000) compared orchiopey patients with herniotomy patients wherein all study patients received ilioinguinal nerve block and/or wound infiltration for analgesia⁴. They found that although orchiopey patients complained more pain after discharge to home, incidence of 1-2 vomits (23%-28%) was similar after orchiopey or herniotomy. In their review and meta-analysis, Baird et al. (2013) did not document anything about nausea/retching/vomiting except for a fleeting mention about nausea and vomiting as a complication after caudal block compared to other analgesic techniques used for inguinal hernia surgeries⁹. However, Shanthanna et al. (2014) in their review and meta-analysis investigated the incidence of nausea-vomiting after caudal block compared to wound infiltration and reported them to be similar with statistically insignificant relative risk (RR=0.77; [0.36, 1.64])¹⁰. Compared to the abovementioned studies performed over last four decades, our study demonstrated higher incidence of nausea/retching/vomiting at home after incisional field block (36%) and lower incidence of nausea/retching/vomiting at home after caudal block (9%) (Table 4).

The core concept inspiring our research was that surgical dissection related unavoidable manipulation of sensitive organs like eye globe, breasts and testicles leads to neural outflow that induces discomforting nausea/retching/vomiting. To interrupt this neural outflow, these sensitive organs may need to be locally anesthetized so that these postsurgical patients have reduced incidence of nausea/retching/vomiting. However, this interruption in neural outflow has to be preemptively performed before the surgical dissection has been initiated because post-surgical interventions may not undo these effects (oculo-cardiac, mammo-vagal and orchio-vagal) after these organs have already been surgically handled and

manipulated intraoperatively^{11-12,22-24}.

Our research primarily focused on the telephone call data points because our aim was to delve into the incidence of nausea/retching/vomiting and rescue anti-emetic/analgesic use during the initial 48-hours upon discharge to home after outpatient pediatric testicular surgery. Although pre-surgical incisional field blocks were not included in our research methods because they are not standard procedures for pediatric testicular surgeries at our institution²⁵, it will be interesting to see in the future if there is any preemptive anti-emetic role of pre-surgical incisional field blocks during testicular surgeries as similar to anti-emetic role of preemptively performed caudal blocks.

It was interesting to note that because of the extended three year period (2013-2016) over which the patients were enrolled into our study, 26% participants used codeine on first postoperative day because they were enrolled during the first half of three year period. Codeine's consumption by participants changed during the second half of three year period because codeine prescription among postsurgical pediatric patients was abandoned per our updated intra-&-inter-departmental policy when U.S. Food & Drug Administration (FDA) introduced a warning against codeine use in children undergoing tonsillectomy

and/or adenoidectomy (2013) and followed up with statement for ongoing evaluation against codeine use as analgesic and antitussive in children younger than 18 years (2015) before finally contraindicating codeine use as analgesic and antitussive in children younger than 12 years (2017)²⁶⁻²⁸.

There were few limitations to our current study. Due to the reasons elicited in our results section, thirty participants were excluded which could have been avoided. The data from all 120 participants could have increased our study's statistical power and our results' validity. Moreover, instead of post-surgical incisional field block, pre-surgical incisional field block might have provided better comparison for pre-surgical caudal block.

Conclusion

On the first postoperative day among boys who had undergone bilateral scrotal and/or inguinal incisions for orchiopexy, a pre-surgical caudal block significantly decreased the incidence of nausea/retching/vomiting compared to post-surgical incisional field block.

References

- BRAMWELL RG, BULLEN C, RADFORD P: Caudal block for postoperative analgesia in children. *Anaesthesia*; 1982, 37:1024-8.
- LAFFERTY PM, GORDON NH, WINNING TJ: A comparison of postoperative pain relief techniques in orchidopexy. *Ann R Coll Surg Engl*; 1990, 72:7-8.
- BROWN TC, EYRES RL, MCDUGALL RJ: Local and regional anaesthesia in children. *Br J Anaesth*; 1999, 83:65-77.
- HO D, KENEALLY JP: Analgesia following paediatric day-surgical orchidopexy and herniotomy. *Paediatr Anaesth*; 2000, 10:627-31.
- HONG JY, HAN SW, KIM WO, CHO JS, KIL HK: A comparison of high volume/low concentration and low volume/high concentration ropivacaine in caudal analgesia for pediatric orchiopexy. *Anesth Analg*; 2009, 109:1073-8.
- MARJANOVIC V, BUDIC I, STEVIC M, SIMIC D: A comparison of three different volumes of levobupivacaine for caudal block in children undergoing orchidopexy and inguinal hernia repair. *Med Princ Pract*; 2017, 26:331-6.
- FELL D, DERRINGTON MC, TAYLOR E, WANDLESS JG: Paediatric postoperative analgesia. A comparison between caudal block and wound infiltration of local anaesthetic. *Anaesthesia*; 1988, 43:107-10.
- SCHINDLER M, SWANN M, CRAWFORD M: A comparison of postoperative analgesia provided by wound infiltration or caudal analgesia. *Anaesth Intensive Care*; 1991, 19:46-9.
- BAIRD R, GUILBAULT MP, TESSIER R, ANSERMINO JM: A systematic review and meta-analysis of caudal blockade versus alternative analgesic strategies for pediatric inguinal hernia repair. *J Pediatr Surg*; 2013, 48:1077-85.
- SHANTHANNA H, SINGH B, GUYATT G: A systematic review and meta-analysis of caudal block as compared to noncaudal regional techniques for inguinal surgeries in children. *Biomed Res Int*; 2014, 2014:890626.
- BANSAL P, SAXENA KN, TANEJA B, SAREEN B: A comparative randomized study of paravertebral block versus wound infiltration of bupivacaine in modified radical mastectomy. *J Anaesthesiol Clin Pharmacol*; 2012, 28:76-80.
- GUPTA D: Regional blocks for pre-emptive anti-emesis. *J Anaesthesiol Clin Pharmacol*; 2012, 28:535-6.
- BHATNAGAR S, GUPTA D, MISHRA S, SRIKANTI M, SINGH M, ARORA R: Preemptive antiemesis in patients undergoing modified radical mastectomy: oral granisetron versus oral ondansetron in a double-blind, randomized, controlled study. *J Clin Anesth*; 2007, 19:512-6.
- AHISKALIOGLU A, YAYIK AM, AHISKALIOGLU EO, EKINCI M, GÖLBOYU BE, CELIK EC, ET AL: Ultrasound-guided versus conventional injection for caudal block in children: A prospective randomized clinical study. *J Clin Anesth*; 2018, 44:91-6.
- SINHA C, KUMAR A, SHARMA S, SINGH AK, MAJUMDAR S, KUMAR A, ET AL: Ultrasound assessment of cranial spread during caudal blockade in children: Effect of different volumes of local anesthetic. *Saudi J Anaesth*; 2017, 11:449-53.
- LUNDBLAD M, EKSBORG S, LÖNNQVIST PA: Secondary spread of caudal block as assessed by ultrasonography. *Br J Anaesth*; 2012, 108:675-81.
- BUVANENDRAN A, FIALA J, PATEL KA, GOLDEN AD, MORIC M, KROIN JS: The incidence and severity of postoperative pain following inpatient surgery. *Pain Med*; 2015, 16:2277-83.
- GAN TJ: Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res*; 2017, 10:2287-98.
- WILLIAMS G, BELL G, BUYS J, MORIARTY T, PATEL A, SUNDERLAND R, ET AL: The prevalence of pain at home and its consequences in children following two types of short stay surgery: a multicenter observational cohort study. *Paediatr Anaesth*; 2015, 25:1254-63.
- MOSSETTI V, BORETSKY K, ASTUTO M, LOCATELLI BG, ZURAKOWSKI D, LIO R, ET AL: Persistent pain following common outpatient surgeries in children: A multicenter study in Italy. *Paediatr Anaesth*; 2018, 28:231-6.
- FEINLEIB J, KWAN LH, YAMANI A: Postoperative nausea and vomiting. Edited by Holt NF, Davidson A, Crowley M. UpToDate. Waltham, MA: UpToDate Inc. Last updated September 25, 2018. Available at: <https://www.uptodate.com/contents/postoperative-nausea-and-vomiting> Accessed on May 6, 2019.
- COVENEY E, WELTZ CR, GREENGRASS R, IGLEHART JD, LEIGHT GS, STEELE SM, ET AL: Use of paravertebral block anesthesia in the surgical management of breast cancer: experience in 156 cases. *Ann Surg*; 1998, 227:496-501.
- KHURANA I, SHARMA R, KHURANA AK: Experimental study of oculocardiac reflex (OCR) with graded stimuli. *Indian J Physiol Pharmacol*; 2006, 50:152-6.
- MENNELLA JA, PEPINO MY: Breast pumping and lactational state exert differential effects on ethanol pharmacokinetics. *Alcohol*; 2010, 44:141-8.
- OLANIPEKUN SO, ADEKOLA OO, DESALU I, KUSHIMO OT: The effect of pre-incision field block versus post-incision inguinal wound infiltration on postoperative pain after paediatric herniotomy. *Open Access Maced J Med Sci*; 2015, 3:666-71.
- FDA Drug Safety Communication: Safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy. Last updated February 20, 2013. Available at: <http://wayback.archive-it.org/7993/20170722185707/https://www.fda.gov/Drugs/DrugSafety/ucm339112.htm> Accessed on May 6, 2019.
- FDA Drug Safety Communication: FDA evaluating the potential risks of using codeine cough-and-cold medicines in children. Last updated July 1, 2015. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluating-potential-risks-using-codeine-cough-and-cold-medicines> Accessed on May 6, 2019.
- FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Last updated April 20, 2017. Available at: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and> Accessed on May 6, 2019.